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Copper complexes with dissymmetrically substituted bis(thiosemicarbazone) ligands as a basis for PET radiopharmaceuticals: control of redox potential and lipophilicity

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Abstract

Copper (II) bis(thiosemicarbazone) derivatives have been used extensively in positron emission tomography (PET) to image hypoxia and blood flow and to radiolabel cells for cell tracking. These applications depend on control of redox potentials and lipophilicity of the bis(thiosemicarbazone) complexes, which can be adjusted by altering peripheral ligand substituents. This paper reports the synthesis of a library of new dissymmetrically substituted bis(thiosemicarbazone) ligands by controlling the condensation reactions between dicarbonyl compounds and 4-substituted-3-thiosemicarbazides or using acetal protection. Copper complexes of the new ligands have been prepared by reaction with copper acetate or *via* transmetallation of the corresponding zinc complexes, which are convenient precursors for the rapid synthesis of radio-copper complexes. Well-defined structure-activity relationships linking ligand alkylation patterns with redox potential and lipophilicity of the complexes are reported.

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Introduction

^{64}Cu or ^{62}Cu complexes with bis(thiosemicarbazonate) ligands can be used as tracers for PET (positron emission tomography) for imaging hypoxic tissues,[1-4] cerebral[5] and myocardial perfusion,[6-9] changes in brain trafficking of copper associated with neurological disease,[10,11] and for cell labelling.[12] For imaging hypoxia, Cu-diacetyl-*bis*(N4-methylthiosemicarbazonate) (Cu-ATSM, labelled with ^{64}Cu or ^{62}Cu), has been widely evaluated clinically.[13] The 12.7-h half-life of ^{64}Cu allows it to be used in centres distant from site of radionuclide production.[14] The mechanism of trapping within cells, whether hypoxia-selective or non-selective, relies on the complexes being neutral and membrane permeable, allowing them to freely diffuse into and out of cells. When in cells the complexes are converted by intracellular reducing agents to putative Cu(I)-BTSC intermediates that can rapidly dissociate, leading to intracellular trapping of the released copper. In normoxic cells Cu(I)-ATSM is capable of resisting Cu(I) dissociation long enough to be re-oxidised by molecular oxygen to Cu(II)-ATSM, which is free to diffuse back out of the cells. However, in hypoxic cells this re-oxidation is slow, allowing dissociation and hence hypoxia-selective trapping within the cells.[1,7,13,15-19] On a slower time-scale, native Cu-trafficking mechanisms can wash the trapped copper out of the cells, preventing prolonged copper retention despite the presence of hypoxia.[20]

The biological behaviour and selectivity of copper bis(thiosemicarbazone) complexes depends on many factors including lipophilicity, planarity, molecular weight, pK_a and redox potential.[21,22] Investigations into the structure-activity relationships of copper bis(thiosemicarbazone) complexes have shown that the substituents at the diimine backbone (Fig. 1, Q_1 and Q_2 positions) are the primary determinants of the redox potential of the complex.[21-24] Replacing hydrogen at Q_1 and Q_2 progressively lowers the Cu(I/II) redox potential by about 60 mV per alkyl group. Alkyl substitutions on the terminal amino groups (R_1, R_2, R_3 and R_4) have less effect on the Cu(I/II) redox potential, but do control lipophilicity.[22] Low redox potentials (i.e. below -0.5 V vs. Ag/AgCl reference electrode) were found to be essential for hypoxic selectivity.[22] There is further scope for tuning of properties to obtain optimal complexes for the various applications.[25,26] The value of subtle changes to the alkyl substitution patterns[22] in improving biological properties for specific applications is illustrated by recent reports of improved hypoxia imaging properties for cardiological applications.[3,27] In this work, therefore, we aimed to extend the range of alkyl substitution patterns within the ligand from which to choose complexes with optimised properties tailored to different uses, by introducing dissymmetric ligands with two different thiosemicarbazone arms.

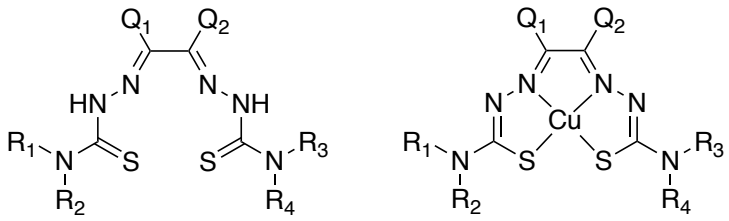

Fig. 1 Structure of bis(thiosemicarbazone) and its copper complex, with substituent nomenclature; R_1, R_2, R_3, and R_4 are alkyl, aryl or hydrogen; Q_1 and Q_2 are alkyl or hydrogen.

Bis(thiosemicarbazone) pro-ligands are described here as symmetric when the substituents on the two terminal nitrogens are the same, and dissymmetric when the substituents on the terminal nitrogens are dissimilar ($NR_1R_2 \neq NR_3R_4$). Almost all ligands evaluated in PET imaging to date are

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symmetric in this respect. Dissymmetric ligands can be further classified as singly dissymmetric or doubly dissymmetric with respect to the backbone substituents Q_1 and Q_2. When the substituents on the backbone are identical (Q_1=Q_2) they can be classed as singly dissymmetric and if they are dissimilar (Q_1≠Q_2) they are doubly dissymmetric.

Symmetric pro-ligands[7,22,26,28-34] are typically synthesised by addition of at least two equivalents of a 4-substituted-thiosemicarbazide to a vicinal diketone under acid catalysis. The synthesis of dissymmetric bis(thiosemicarbazone) pro-ligands, first reported by Green and co-workers,[35] has been reviewed.[36] The most generally applicable approach involves protection of one of the carbonyl groups, for example reacting isonitroacetone with a chosen thiosemicarbazide (Fig. 2) giving an intermediate which is then deprotected and reacted with a second (dissimilar) thiosemicarbazide. Lim *et al.* reported[35] that this method gave a mixture of symmetric and dissymmetric bis(thiosemicarbazones). Similarly, use of acetal protection to control reaction with the first thiosemicarbazide,[35,37,38] followed by hydrolysis of the acetal before treating with the second, has been reported for Q_1 = CH_3 and Q_2 = H (Fig. 2). Hydrolysis of the imine group during the deprotection step can be avoided by using the mild Lewis acid lithium tetrafluoroborate ($LiBF_4$) as the catalyst (Fig. 2).[35] Stepwise addition of two thiosemicarbazides to an unprotected diketone (Fig. 2) has also been used. The mono(thiosemicarbazone) formed initially precipitates and can be isolated and reacted with a second thiosemicarbazide under more forcing conditions.[39,40] This method has been used to make dissymmetric bis(thiosemicarbazone) pro-ligands with Q_1 = Q_2 = Me,[30,39-44] and Q_1 = Me, Q_2 = H[36,39] but yields mixed bis(thiosemicarbazone) proligands and cyclic by-products in some cases.[45] Cyclisation[25,26,46,47] of the intermediate may also occur. Dissymmetric bis(thiosemicarbazone) proligands have been reported in which one side arm is modified to improve water solubility (using a carbohydrate[48] or sulfonate[39]), introduce fluorescence[49] or radiolabel with fluorine-18.[50] These pro-ligands were derived from a dissymmetric bis(thiosemicarbazone) in which one thiosemicarbazide arm is a thiocarbohydrazide[40,42-44,51] (Fig. 2).

The aims of the present work were to expand the available library of BTSC complexes to include more dissymmetric ones from which to choose fine-tuned properties for PET applications, evaluate transmetallation as a method to synthesise the copper complexes from the zinc (II) complexes, and measure the effects of the resulting different alkylation patterns on redox potential and lipophilicity.

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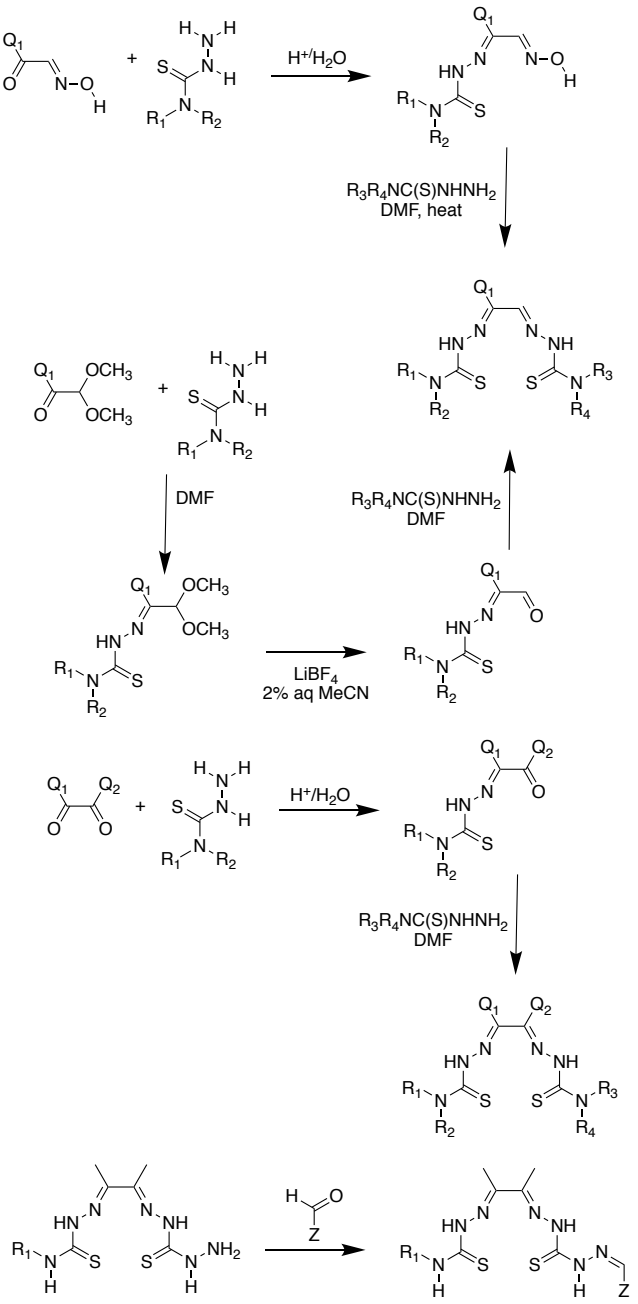

Fig. 2. Literature routes for synthesis of dissymmetric bis(thiosemicarbazone) pro-ligands using isonitrone or acetal protection and using unprotected diketones, and dissymmetric functionalisation via a thiocarbohydrazide side arm.

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Results and Discussion

BTSC ligands with two different thiosemicarbazone arms were synthesised via a range of strategies as described below, with less than 5% contamination by scrambled or symmetric proligands unless otherwise noted. Mono(thiosemicarbazone) intermediates, listed in Table 1, are referred to by a letter designation **A** – **M**, while bis(thiosemicarbazone) pro-ligands (Table 2) are referred to by a numeric designation **1** – **36**. When used to define their Cu(II) and Zn(II) complexes, the numeric designation implies coordination in the form of the doubly-deprotonated dianion. BTSC ligands with two identical thiosemicarbazone arms (**1, 2, 5, 6, 7, 8, 20, 21, 25**) were prepared following a previously reported procedure[22] and obtained in high yield and purity.

Synthesis of Pro-ligands via Protected Dicarbonyls

Using the method of Green[35] (Fig. 3), 4-methyl-3-thiosemicarbazide was reacted with methylglyoxal-1,1-dimethylacetal in DMF to give **A**, which was deprotected to give **B** (and **D** was prepared analogously from **C**). However, **B** was more conveniently prepared directly by aqueous reaction of 4-methyl-3-thiosemicarbazide with methylglyoxal-1,1-dimethylacetal; **H** and **I** were directly prepared analogously from methylglyoxal-1,1-dimethylacetal. **B** was reacted with thiosemicarbazide to afford the known dissymmetric pro-ligand **3**[35] in 6% overall yield. Again in a similar manner to Green, reversing the order of thiosemicarbazide addition gave intermediates **C** and **D** and pro-ligand **4**[35] in 4% overall yield. Applying this strategy to 3,3-dimethoxy-2-butanone to prepare **E** required use of ethanol as the reaction solvent followed by extraction with diethyl ether. Intermediate **E** is a precursor to **F**, which has been more conveniently prepared by Holland *et al.* using the diketone route (Fig. 2).[40]

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Table 1. Mono(thiosemicarbazone) intermediates. R_1, R_2, Q_1 and Q_2 refer to substituents as defined in Figs. 1 and 2; X designates whether the non-reacting carbonyl group is protected as the dimethylketal or not.

Compound	R_1	R_2	Q_1	Q_2	X
A	Me	H	Me	H	$(OMe)_2$
B	Me	H	Me	H	=O
C	H	H	Me	H	$(OMe)_2$
D	H	H	Me	H	=O
E	H	Me	Me	Me	$(OMe)_2$
F	H	Me	Me	Me	=O
G	H	H	Me	Me	=O
H	Et	H	Me	H	=O
I	Ph	H	Me	H	=O
J	Me	Me	Me	Me	=O
K	H	H	Me	Et	=O
L	Me	H	Me	Et	=O
M	Et	H	Me	Et	=O

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Table 2. Redox and lipophilicity properties of copper(II) complexes. *derived from literature values.

Pro-ligand	R_1	R_2	Q_1	Q_2	R_3	R_4	$E(\Delta E_p)$ $Cu^{I/II}$ (mV)	$E(\Delta E_p)$ $Cu^{II/III}$ (mV)	logP	reference
1	Me	H	H	H	H	Me	-960(65)	220(170)	1.28	22, 11, 33, 56, 57
2	Et	H	H	H	H	Et	-1060(63)	130(131)	1.58	33
3	Me	H	Me	H	H	H				35
4	H	H	Me	H	H	Me				35
5	Me	H	Me	H	H	Me	-1040*		1.52*	22, 56, 60
6	Me	Me	Me	H	Me	Me	-1060*			22
7	Et	H	Me	H	H	Et	-1050*		1.74*	22, 60
8	Ph	H	Me	H	H	Ph				22
9	Me	H	Me	H	Me	Me	-1010(73)	240(97)	1.70	35
10	Me	H	Me	H	H	Et				new
11	Et	H	Me	H	H	Me	-1080(72)	180(90)	1.64	new
12	Me	H	Me	H	H	Ph	-930(69)		1.91	new
13	Et	H	Me	H	H	H				new
14	Et	H	Me	H	Me	Me	-1050(68)	200(95)	1.81	new
15	Et	H	Me	H	H	Ph	-1060(60)		1.98	new
16	Ph	H	Me	H	H	H				new
17	Ph	H	Me	H	H	Me	-1040(93)		1.87	new
18	Ph	H	Me	H	Me	Me				new
19	Ph	H	Me	H	H	Et	-970(61)		1.97	new
20	Me	H	Me	Me	H	Me	-1120(90)	190(81)	1.69*	22, 56, 57, 60
21	Et	H	Me	Me	H	Et	-1130(88)	180(84)	1.86*	58, 60
22	Me	H	Me	Me	Me	Me	-1050(65)	260(87)	1.87	30
23	H	H	Me	Me	H	Me	-1120(75)	180(83)	1.49	new
24	H	H	Me	Me	Me	Me	-1130(79)	190(82)	1.68	new
25	H	H	Me	Et	H	H	-1160(51)	140(66)	1.40	22, 56, 60, 3, 27
26	H	H	Me	Et	H	Me	-1130(74)	140(84)	1.63	new
27	H	H	Me	Et	Me	Me	-1100(72)	180(80)	1.81	new
28	H	H	Me	Et	H	Et	-1110(72)	170(79)	1.73	new
29	Me	H	Me	Et	H	H	-1130(73)	150(81)	1.61	new
30	Et	H	Me	Et	H	H	-1140(53)	210(66)	1.72	new
31	Me	H	H	H	H	Me	-960*			22, 56, 10, 11
32	H	H	Me	H	H	H	-1030*	220*		22, 56
33	H	H	Me	Me	H	H	-1120*	170*		22, 56, 3, 27
34	Me	H	Me	Et	H	Me	-1110*	190*		22, 56
35	H	H	Et	Et	H	H	-1120*	160*		22, 56, 3
36	Me	H	Et	Et	H	Me	-1110*	180*	2.01*	22, 56

Reaction of thiosemicarbazide with 3,3-dimethoxy-2-butanone in DMF in the presence of molecular sieves unexpectedly led directly to ketone **G** without isolation of the diacetal. Reaction of **G** with 4-methyl-3-thiosemicarbazide gives the new dissymmetric pro-ligand **23** in good yield. This outcome prompted evaluation of methylglyoxal-1,1-dimethylacetal as a commercially available precursor that is cheaper and more convenient than pyruvic aldehyde. Thus, known symmetric pro-ligands **5**, **6** and **7**[52] were prepared by reaction with two equivalents of the appropriate thiosemicarbazide with methylglyoxal-1,1-dimethylacetal. The new pro-ligand **8** was also prepared by this method.

Using the same approach dissymmetric pro-ligands can be obtained via the intermediate aldehydes derived from the corresponding dimethylacetal. Reaction of **B** with the appropriate thiosemicarbazide affords the known compounds **3**,[35] **9**,[53] **10**[37] and the new compound **12**. ^{1}H NMR spectroscopy indicates that some scrambling occurs during these reactions, thus for example **12** contains 3% of both symmetric ligands with methyl or phenyl groups at the terminal positions (see supplementary information for spectroscopic evidence of contamination, or lack of it, of pro-ligands by isomers and scrambled products). The intermediate **H** has been previously reported[38] and was used here to synthesise the new dissymmetric pro-ligands **13** and **14** efficiently, as well as the previously reported **11**.[38] The new intermediate **I** was used to prepare new dissymmetric pro-ligands **16**, **17, 18** and **19**. Reaction of **H** with 4-phenyl-3-thiosemicarbazide similarly gave the desired **15** but significantly contaminated (10%) with the symmetric proligand **8**. Similarly, reaction of **I** with 4,4-dimethyl-3-thiosemicarbazide produced the desired **18** contaminated with 25% of the known proligand **6**.

Synthesis of Pro-ligands via Unprotected Diketones

Dissymmetric pro-ligands can be prepared from 2,3-butanedione via mono-substituted-3-thiosemicarbazone intermediates (Fig. 2). Reaction of 2,3-butanedione with one equivalent of thiosemicarbazide, 4-methyl-3-thiosemicarbazide or 4,4-dimethyl-3-thiosemicarbazide affords **G**, **F**[40] and **J**, respectively. Reaction of **F** with thiosemicarbazide, and **G** with 4,4-dimethyl-3-thiosemicarbazide, affords the new pro-ligands **23** and **24** respectively in good yield and purity. **23** could also be prepared by addition of the thiosemicarbazide arms in the reverse order, i.e. reaction of **F** with thiosemicarbazide; similarly, **22** was prepared by reaction of **F** with 4,4-dimethyl-3-thiosemicarbazide.

Doubly dissymmetric pro-ligands could be synthesised by exploiting the reactivity difference between the ethyl and methyl ketone functionalities of 2,3-pentanedione: reaction with thiosemicarbazide affords **K** (in which the reaction has occurred at the methyl ketone) in 66% yield with a 9% impurity in which the thiosemicarbazide reacted with the ethyl ketone. Similarly, reactions with 4-methyl-3-thiosemicarbazide and 4-ethyl-3-thiosemicarbazide afford **L** and **M** with 4% and 10% impurities respectively. Given this high degree of selectivity, the ethyl ketone intermediates were reacted with further thiosemicarbazides to afford new doubly asymmetric pro-ligands **26**, **27**, **28**, **29** and **30**, with less than 5% of the minor isomers with the position of the arms reversed (see supplementary information).

Synthesis of Complexes

Known Cu-BTSC complexes were synthesised and purified following a previously reported protocol.[22] Similarly reactions of the dissymmetric pro-ligands **12**, **14**, **16**, **17**, **23**, **24**, **26**, **27**, **28**, **29**

and **30** with copper (II) acetate in water afforded a range of new bis(thiosemicarbazone) copper complexes which were characterised by IR and Raman spectroscopy, elemental analysis, UV-vis spectroscopy, and mass spectroscopy; the colour, solubility and all analytical and spectroscopic data including vibrational and electronic spectra were consistent with 1:1 Cu(II) complexes with the expected planar, four coordinate structure described for previously reported members of the series.[22,57] Despite some proligands having minor contamination with isomers or "scrambled" proligands, HPLC indicated that complexes were largely free of contamination by isomeric or scrambled complexes unless otherwise indicated.

Zinc bis(thiosemicarbazone) complexes can be used as precursors for copper bis(thiosemicarbazone) complexes by transmetallation with copper acetate in water.[40] This is a quick and convenient approach for radiolabelling BTSC ligands with radiocopper, demonstrated by the attachment of a zinc bis(thiosemicarbazone) complex to a solid support via an axial pyridyl ligand, and eluting with a [^{64}Cu]Cu-acetate solution.[54,55] As well as providing a simple radiolabelling methodology, the solid support-based transmetallation approach offers the advantage that the concentration of free ligand in the final product is low because unused ligand is retained on the column.[54] Treatment of zinc acetate with bis(thiosemicarbazone) proligands in refluxing ethanol gave the zinc complexes as yellow or orange precipitates. Spectroscopic properties were consistent with 1:1 complexes without additional ligands. Reaction of the Zn(II) complexes Zn(**14**), Zn(**17**) or Zn(**29**) with copper acetate monohydrate afforded the corresponding Cu(II) complexes, as confirmed by IR, Raman and mass spectroscopy, in good yield. The zinc complexes are a convenient and stable form in which to store the ligands for future synthesis of the copper complexes or for radiolabelling, and their simple isolation provides a useful means to obtain them free of their precursors and by-products.

Electrochemistry

Cyclic voltammetry was performed on all complexes whose HPLC indicated sufficient purity (i.e. <5% contamination with possible scrambled or isomeric complexes) using a glassy carbon working electrode with ferrocene as an internal standard. Table 2 shows the electrochemical reduction and oxidation potentials, along with peak separations of the reductive and oxidative waves, of complexes determined in this work (**Cu(1), Cu(2), Cu(9), Cu(11), Cu(12), Cu(14), Cu(15), Cu(17), Cu(19), Cu(20), Cu(21), Cu(22), Cu(23), Cu(24), Cu(25), Cu(26), Cu(27), Cu(28), Cu(29), Cu(30)**). All complexes measured showed a quasi-reversible one-electron reduction (e.g., Fig. 3). In addition, quasi-reversible Cu(II/III) processes were observed whose potentials could be similarly determined in some cases. Measurement of the Cu(I/II) electrode potentials of **Cu(1)**, **Cu(20)** and **Cu(25)**, whose electrochemistry has been reported previously,[22,56,57,58] enabled combination and comparison of the new data with previously published data, by correcting the difference in reference electrode (subtracting 530 mV from values in ref. 22). These previously published data are also included, after adjustment in this way, in Table 2 (denoted with asterisk). The structure-activity relationships were in accord with previous observations[22,56,57,58] (Fig. 4), showing that the dissymmetric complex Cu(I/II) redox potentials, like those of the previously reported symmetric ones, correlated (R^2 = 0.74) with the number of alkyl groups at Q_1 and Q_2 (with Cu(I/II) redox potentials lowered by 66 mV per alkyl group, as determined from the regression line in Fig. 4). As observed previously,[22] compounds with phenyl groups instead of alkyl groups at the terminal positions proved to include outliers and were excluded from the correlation in Fig. 4. Those compounds with two alkyl groups at the Q_1 and Q_2 positions showed low and tightly-grouped Cu(I/II) redox potentials (Fig. 4). In contrast, the spread of

Cu(II/III) redox potentials was much less and there was no clear correlation with alkylation at Q_1 and Q_2 (R^2 = 0.02) or $R_1 - R_4$. Even within groups of compounds with the same number of alkyl groups at Q_1 and Q_2, the effect of the number of terminal alkyl groups on Cu(I/II) redox potentials was small (13 mV per alkyl group for compounds with alkyl groups at both Q_1 and Q_2) and poorly correlated (R^2 = 0.35) (supplementary data, Fig. S22). To ensure that the conformity of the redox behaviour of the new compounds to the trends previously observed[22,56] was not unduly influenced (and hence invalidated) by including the published data, we also plotted the new Cu(I/II) redox potentials alone; the correlation was similar to that derived from the combined data set, with a 59 mV lowering of the potential per alkyl group at Q_1/Q_2 (R^2 = 0.64) (see supplementary data, Fig. S23), similar to the average shift of around 60 mV per alkyl group observed previously.[22]

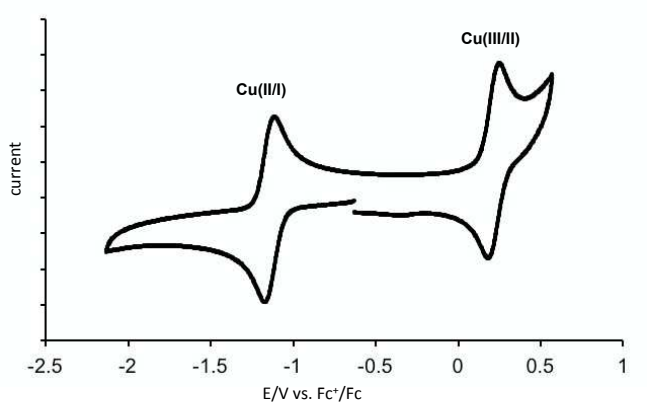

Fig. 3. Exemplar cyclic voltammogram of **Cu(30)** in deoxygenated anhydrous DMSO/0.1 M $[Bu_4N][BF_4]$ at 0.1 V/s scan rate.

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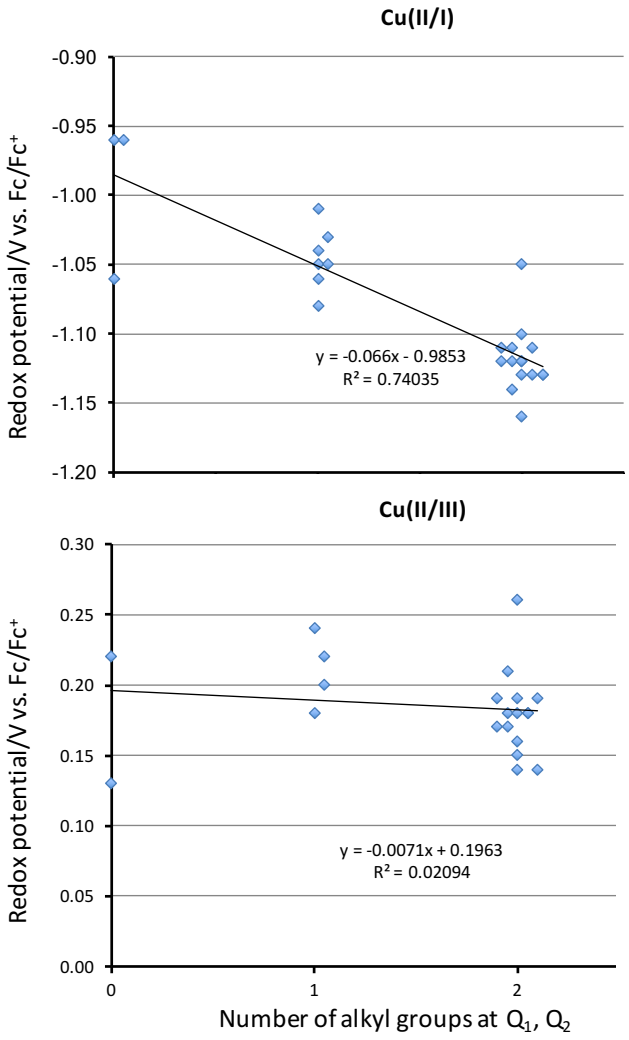

Fig. 4. Correlation, with regression lines, of Cu(I/II) (top) and Cu(II/III) (bottom) redox potentials with alkylation at Q_1 and Q_2. Some points have been offset slightly horizontally for visual clarity. All available data are included, from this work and literature data (corrected for different referencing), with the exception of compounds containing phenyl groups.

LogP measurement

Reversed-phase HPLC was used to estimate the lipophilicity of the newly synthesised Cu-BTSC complexes as an alternative to octanol-water partitioning. Lipophilicity assessment by reversed-phase HPLC assumes a linear relationship between the logarithm of the retention factor of the compound (logK)[59] and its logP. Thus, reference Cu-BTSC complexes (**Cu(20)**, **Cu(21)**, **Cu(5), Cu(7)** and **Cu(36)**[60]) were chromatographed and their experimental logK values correlated directly with their known experimental logP values (from octanol water extraction experiments[60]) to create a calibration curve (see Figure 5), which was indeed linear and was used to calculate the logP values of the new Cu-BTSC complexes, which are summarised in Table 2 (with those used for the calibration marked with an asterisk). As expected, higher logP values correlated with greater molecular weight, with complexes having phenyl groups in their structure being the most lipophilic. Although the effect of alkylation on logP is expected to vary with location and identity of the alkyl/aryl group, it is clear that alkylation of both the diimine backbone and pendant amino arms contributed to enhancing the

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lipophilicity of Cu-BTSCs (by 0.16 per alkyl group on average, from linear least squares regression of logP and total number of alkyl groups at $R_1 – R_4$ and $Q_1 – Q_2$; see supplementary information, Fig. S24).

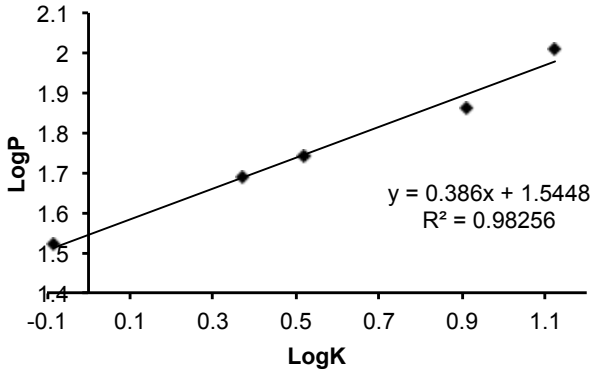

Fig. 5 Correlation between the literature logP values[60] of **Cu(20), Cu(21), Cu(5), Cu(7) and Cu(36)** and their experimental logK values measured by HPLC. A C_{18} column was used as the stationary phase and a water + 0.1 % TFA (60%)/acetonitrile + 0.1 % TFA (40%) isocratic mobile phase.

Recent mechanistic studies with hypoxia-targeting copper(II) bis(thiosemicarbazone) complexes, combined with *in vivo* studies in rodent tumour models, suggest that the combination of redox potential and lipophilicity offered by CuATSM (**Cu(20)**) may not be ideal for hypoxia imaging and that less lipophilic complexes may give improved pharmacokinetics. In particular, CuATS (**Cu(33)**)and CuCTS (**Cu(25)**) showed improved clearance from non-hypoxic tissue and superior hypoxic-to-normoxic tissue uptake ratio, as well as a more favourable pO_2 threshold of selectivity, warranting *in vivo* evaluation for cardiac hypoxia imaging, based on experiments in the Langendorff isolated perfused rat heart model.[3,27] Both have a similar redox potential but reduced lipophilicity compared to CuATSM. By including complexes with dissymmetric ligands, which are now accessible by the methods described here, the library of compounds for biological evaluation with lipophilicity and redox potential similar to CuATS and CuCTS can be extended to allow selection of optimal complexes for hypoxia imaging in different clinical contexts. In particular, **Cu(23)**, **Cu(24)**, **Cu(26)** and **Cu(29)**, among these compounds, should be evaluated biologically as they have logP values comparable to those of CuATS and CuCTS and slightly lower than that of CuATSM, and Cu(I/II) redox potentials in the appropriate range.

Conclusions

This paper reports the synthesis of new dissymmetrically substituted bis(thiosemicarbazone) ligands in high purity by controlling the condensation reactions between dicarbonyl compounds and 4-substituted-3-thiosemicarbazides or using acetal protection. Ready access to dissymmetric pro-ligands extends the library of complexes that have suitable properties for hypoxia imaging and from which optimal imaging agents can be selected. Copper complexes of the new ligands have been prepared by reaction with copper acetate or via transmetallation of the corresponding zinc complexes, which are convenient precursors for the rapid synthesis of the copper (and radiocopper) complexes. The new dissymmetric complexes display reduction potentials that correlate with the

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number of backbone (Q_1, Q_2) alkyl groups, as seen previously for the symmetric complexes, and extend the range of lipophilicity values available.

Experimental

All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Interlink Scientific Services and VWR International Ltd. and used without further purification, unless otherwise stated. NMR analysis was undertaken in d^6-DMSO using a JEOL NMR ECS-400 and JEOL Delta v5.02 software operating at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C {^{1}H} spectra. Spectra were reference to residual solvent and *J* values are given in Hz. FTIR spectra were obtained using a Shimadzu IR Affinity-1 Fourier Transform Infrared Spectrometer with a Golden Gate Diamond Attenuated Total Reflectance (ATR) attachment. CHN analyses were obtained at the Science Centre, London Metropolitan University utilising a Carlo Erba Flash 2000 elemental analyser. Raman spectra were obtained using a Horiba LabRAM-HR Raman spectrometer utilising lasers operating at 532.00, 632.81 or 784.15 nm. A ×50 objective lens was used giving a beam diameter of approximately 2 µm on the sample. The spectrometer was calibrated against the silicon line at 520.6 cm^{-1}. UV-visible spectra were obtained with a Shimadzu UV-1800 spectrometer. A Bruker micrOTOF-Q mass spectrometer was used to record positive mode ESI mass spectra. Samples were dissolved in DMSO at a concentration of 1 mg/ml before being diluted 1 in 100 in methanol. 10 µL of sample solution was injected into a flowing stream of 10 mM ammonium acetate in 95% methanol in water (flow rate: 0.02 mL/min) and the flow directed into the electrospray source of the spectrometer. Data were processed in Bruker's Compass Data Analysis software utilising a lock mass.

Cyclic voltammograms were recorded using a µAUTOLAB potentiostat (Metrohm Autolab B. V., Netherlands) and General Purpose Electrochemical System (GPES) acquisition and analysis software, with a scan rate of 0.1 V/s under argon using a glassy carbon working electrode, a silver wire pseudo-reference electrode and a platinum auxiliary electrode, in DMSO (5 mL) with tetrabutylammonium hexafluorophosphate (0.1 M, Sigma Aldrich) as a support electrolyte and a Cu-complex concentration of 0.5 mM. All potentials were referenced to the internal standard ferrocene/ferrocenium couple. The redox potentials were calculated as the midpoint between the reduction and oxidation peaks.

Reversed phase HPLC was used both to determine purity and lipophilicity (logP) of new copper complexes, using an Eclipse XDB-C_{18} column (4.6 x 150 mm, 5 µm) as the stationary phase and an isocratic mobile phase consisting of water + 0.1 % TFA (60 %) and acetonitrile + 0.1 % TFA (40 %). Cu-BTSC complexes of known logP values (**Cu(10)**, **Cu(11)**, **Cu(21)**, **Cu(22)** and **Cu(23)**), determined by octanol-water extraction[60]) were chromatographed and the logarithms of their retention factors (logK[59]) plotted against their literature logP values to construct a calibration curve. LogK values were calculated using $\log K = \log[(t_r-t_o)/t_o)]$, where t_r is the retention time of the complex and t_o is the retention time of the solvent (DMSO). The resulting linear least-squares regression equation was used to calculate logP values. Thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel TLC plates as the stationary phase and ethyl acetate as the mobile phase.

Proligand precursors A-M

Synthesis of A: 4-methyl-3-thiosemicarbazide (1.315 g, 0.013 mol) was dissolved in DMF (40 mL), followed by the addition of methylglyoxal-1,1-dimethylacetal (1.5 mL, 0.012 mol, 1.5 g). The

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resulting solution was left to stir (3 days). The volume was reduced under vacuum and diethyl ether was added to the resulting viscous oil and cooled on ice overnight. The precipitate was isolated, washed with diethyl ether (4 x 1 mL) and dried. A clear crystalline solid (0.585 g) was recovered (24% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.19 (s, 1 H, N-N*H*), 8.94 (q, 1 H, H_3C-N*H*, J= 4.4 Hz), 4.49 (s, 1 H, O-C*H*), 3.25 (s, 6 H, O-CH_3), 2.93 (d, 3 H, HN-CH_3, J= 4.4 Hz), 1.78 (s, 3 H, N=C-CH_3). ^{13}C {^{1}H} NMR (DMSO-d_6, 100 MHz): δ= 179.57 (*C*=S), 148.60 (*C*=N), 106.87 (H*C*-O), 55.16 (O-*C*H_3), 31.39 (HN-*C*H_3), 11.17 (N=C-*C*H_3). IR (neat): ν_{max}/cm^{-1} 3279 (m), 3227 (w), 2936 (w), 1537 (m), 1504 (m), 1435 (m), 1410 (m), 1366 (m), 1325 (m), 1271 (m), 1213 (m), 1192 (m), 1115 (m), 1072 (s), 1057 (s), 986 (s), 949 (s), 860 (m), 660 (m), 559 (s), 494 (m). Raman (neat), ν_{max}/cm^{-1} 784.15 nm: 1642 (s), 1539 (w), 1499 (w), 1450 (w), 1437 (w), 1324 (w), 1277 (w), 1224 (w), 1156 (w), 1062 (w), 1044 (w), 1022 (w), 985 (m), 963 (w), 860 (s), 799 (s), 660 (w), 632 (w), 582 (m), 573 (s), 495 (w), 435 (w), 354 (w), 308 (m), 272 (m). Mp: >84-88 °C.

Synthesis of B: 4-methyl-3-thiosemicarbazide (2.500 g, 24.0 mmol) was dissolved in de-ionised water (100 mL, 50 °C) and HCl (32%, 5 drops) was added. Methylgloxal-1,1-dimethylacetal (8.70 mL, 72 mmol, 8.49 g) was added rapidly and vigorously stirred (50 °C, 5 minutes). The precipitate was recovered via filtration, washed with de-ionised water (10 x 50 mL) and dried. A yellow solid (2.473 g) was recovered (65% yield). δ_H 11.16 (1 H, s, N-NH), 9.32 (1 H, s, O=CH), 8.98 (1 H, m, J= 4.4, H_3C-N*H*), 2.98 (3 H, d, J= 4.4, HN-CH_3), 1.90 (3 H, s, N=C-CH_3). δ_C 192.10 (C=O), 179.45 (C=S), 145.94 (C=N), 31.67 (HN-CH_3), 9.66 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3350 (m), 3171 (m), 2845 (w), 1692 (m), 1593 (m), 1537 (m), 1504 (s), 1410 (m), 1369 (m), 1200 (s), 1146 (m), 1113 (m), 1047 (s), 1001 (s), 856 (s), 789 (m), 665 (s), 592 (s), 569 (s), 534 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3354 (w), 3179 (w), 2921 (w), 2848 (w), 1696 (m), 1577 (s), 1433 (w), 1278 (w), 1227 (w), 1192 (w), 1116 (w), 1045 (w), 856 (w), 783 (w), 567 (w), 357 (w), 296 (w), 237 (w). Mp: >156 °C (dec.).

Synthesis of C: Freshly activated molecular sieves (3 Å, 0.801 g) was added to DMF (15 mL, 60 °C), followed by the addition of thiosemicarbazide (0.770 g, 0.0084 mol). This was followed by the addition of methylglyoxal-1,1-dimethylacetal (1 mL, 0.0083 mol, 1 g). The resulting solution was left to stir (room temperature, 3 days). The molecular sieves were filtered off and the DMF was removed under vacuum. The crude product was washed with a little diethyl ether and dried. An off white solid (0.769 g) was recovered (48% yield). δ_H 10.21 (s, 1 H, N-N*H*), 8.23 (s, 1 H, C-N*H*), 7.72 (s, 1 H, C-N*H*), 4.48 (s, 1 H, O-C*H*), 3.24 (s, 6 H, O-CH_3), 1.78 (s, 3 H, N=C-CH_3). δ_C 179.90 (*C*=S), 149.02 (*C*=N), 106.78 (H*C*-O), 55.16 (O-*C*H_3), 11.21 (N=C-*C*H_3).

Synthesis of D: Compound **C** (0.754 g, 0.004 mol) was dissolved in an acetonitrile solution (15 mL, 98% acetonitrile, 2% de-ionised water, 60 °C). $LiBF_4$ (0.720 g, 0.008 mol) was added and the resulting solution was left to stir (60 °C, 1 hour). A saturated solution of Na_2CO_3 (30 mL) was added rapidly resulting in the formation of a brown/orange solution. The product was extracted with diethyl ether (1 x 50 mL, 2 x 25 mL) and the organic solution was dried over magnesium sulfateand evaporated to dryness. A brown solid (0.137 g) was recovered (24% yield). δ_H 11.18 (s, 1 H, N-N*H*), 9.32 (s, 1 H, O=C*H*), 9.01 (m, 1 H, H_3C-N*H*), 2.99 (d, 3 H, HN-CH_3, J= 4.8 Hz), 1.90 (s, 3 H, N=C-CH_3). δ_C 192.16 (*C*=O), 179.46 (*C*=S), 145.93 (*C*=N), 31.69 (HN-*C*H_3), 9.68 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3352 (w), 3173 (m), 2963 (w), 2843 (w), 1694 (m), 1593 (m), 1537 (m), 1504 (m), 1410 (m), 1369 (m), 1200 (s), 1146 (m), 1111 (m), 1047 (s), 1001 (s), 856 (m), 789 (m), 665 (s), 594 (s), 569 (s), 534 (s), 503 (m).

Synthesis of E: 4-methyl-3-thiosemicarbazide (0.890 g, 8.5 mmol) was dissolved in ethanol (30 mL, 60 °C), followed by the addition of 3,3-dimethoxy-2-butanone (1.25 mL, 9.3 mmol, 1.23 g). The resulting solution was left to stir at 60 °C for 36 h. The precipitate was filtered off and discarded. The solvent was removed and the resulting solid was extracted with diethyl ether (1 x 50 mL, 2 x 25 mL). The diethyl ether was removed and the remaining solid was dried. A white solid (0.308 g) was recovered (17% yield). δ_H 9.98 (1 H, s, N-NH), 8.01 (1 H, m, H_3C-N*H*), 3.06 (6 H, s, O-CH_3), 2.96 (3 H, d, J = 4.8, HN-CH_3), 1.86 (3 H, s, N=C-CH_3), 1.37 (3 H, s, O-C-CH_3).

Synthesis of F: 4-methyl-3-thiosemicarbazide (0.89 g, 8.5 mmol) was dissolved in de-ionised water (100 mL). The solution was cooled (4 °C) over ice, followed by the addition of HCl (32%, 2 drops). 2,3-butanedione (7.15 mL, 81.5 mmol, 7.01 g) was added rapidly and vigorously stirred at 4 °C for 1 h. The precipitate was recovered via filtration, washed with de-ionised water (3 x 30 mL), ethanol (20 mL, cold), diethyl ether (25 mL, cold) and dried. The crude was recrystallized from ethanol in a freezer. A white crystalline solid (0.684 g) was recovered (60% yield). δ_H 10.61 (1 H, s, N-NH), 8.59 (1 H, q, J = 4.4, H_3C-N*H*), 3.01 (3 H, d, J = 4.4, HN-CH_3), 2.38 (3 H, s, O=C-CH_3), 1.91 (3 H, s, N=C-CH_3). δ_C 198.04 (C=O), 179.49 (C=S), 146.49 (C=N), 31.94 (HN-CH_3), 25.31 (O=C-*C*H_3), 10.57 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3285 (m), 1670 (s), 1593 (w), 1537 (m), 1495 (s), 1427 (m), 1410 (s), 1360 (m), 1207 (s), 1152 (s), 1126 (s), 1105 (s), 1047 (s), 999 (m), 835 (m), 725 (w), 667 (m), 629 (m), 606 (s), 577 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3289 (w), 2919 (w), 1671 (m), 1591 (s), 1409 (w), 1367 (w), 1304 (w), 1213 (w), 1128 (w), 1106 (w), 1000 (w), 947 (w), 836 (w), 725 (w), 609 (w), 578 (w), 318 (w). Mp: >149 °C (dec.).

Synthesis of G: Method 1: Freshly activated molecular sieves (3 Å, 0.808 g) was added to DMF (15 mL, 60 °C), followed by the addition of thiosemicarbazide (0.773 g, 8.5 mmol) and 3,3-dimethoxy-2-butanone (1.5 mL, 11 mmol, 1.48 g). The resulting solution was left to stir at 60 °C for 3 d. The molecular sieves and solid by-products were filtered off, the DMF was removed under vacuum and the sample dried. A brown solid (0.342 g) was recovered (20% yield). Method 2: Thiosemicarbazide (1.55 g, 17.0 mmol) was dissolved in de-ionised water (100 mL, warm). The solution was cooled (5 °C) on ice, followed by the addition of HCl (32%, 20 drops). 2,3-butanedione (5.97 mL, 68.0 mmol, 5.86 g) was added rapidly and vigorously stirred at 5 °C for 10 m. The precipitate was recovered via filtration, washed with de-ionised water (6 x 50 mL) and dried. An off white solid (1.687 g) was recovered (62% yield). δ_H 10.54 (1 H, s, N-NH), 8.67 (1 H, s, C-NH), 8.05 (1 H, s, C-NH), 2.33 (3 H, s, O=C-CH_3), 1.90 (3 H, s, N=C-CH_3). δ_C 198.15 (C=O), 180.27 (C=S), 146.39 (C=N), 25.28 (O=C-*C*H_3), 10.59 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3443 (m), 3323 (m), 3165 (m), 1682 (s), 1587 (s), 1504 (s), 1452 (m), 1418 (m), 1364 (m), 1290 (m), 1107 (s), 1045 (m), 993 (m), 949 (m), 853 (s), 712 (m), 621 (s), 608 (s), 556 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3445 (w), 3323 (w), 3175 (w), 3000 (w), 2956 (w), 2905 (w), 1675 (s), 1605 (s), 1462 (w), 1426 (w), 1371 (w), 1307 (w), 1284 (w), 1107 (s), 1045 (w), 1008 (w), 946 (w), 846 (w), 741 (w), 608 (w), 464 (w), 315 (w), 143 (w). Mp: >173 °C (dec.).

Synthesis of H: 4-ethyl-3-thiosemicarbazide (2.288 g, 19.2 mmol) was dissolved in de-ionised water (200 mL, warm), the insoluble particulates were filtered off and then the solution was cooled to room temperature. HCl was added (32%, 8 drops) followed by the rapid addition of methylglyoxal-1,1-dimethylacetal (6.96 mL, 58.0 mmol, 6.79 g). The solution was vigorously stirred (50 °C, 1 hour). The precipitate was recovered via filtration, washed with de-ionised water (8 x 50 mL) and dried. A pale yellow solid (2.047 g) was recovered (62% yield). δ_H 11.08 (1 H, s, N-NH), 9.34 (1 H, s, O=CH), 9.01 (1 H, t, J = 5.6, H_2C-N*H*), 3.56 (2 H, qd, J = 7.2, 5.6, *H*$_2$C-NH), 1.90 (3 H, s, N=C-CH_3), 1.03 (6 H, t, J

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= 7.2, H_2C-CH_3, J= 7.2). δ_C 191.18 (C=O), 178.41 (C=S), 146.00 (C=N), 39.19 (N-CH_2), 14.54 (H_2C-CH_3), 9.68 (N=C-CH_3). IR: ν_{max}/cm^{-1} 3319 (w), 3142 (m), 2976 (w), 2835 (w), 1688 (s), 1587 (m), 1541 (s), 1489 (m), 1422 (m), 1368 (m), 1279 (m), 1188 (s), 1126 (s), 1086 (m), 1059 (m), 1007 (m), 939 (m), 849 (m), 710 (m), 660 (s), 538 (w). Raman (632.81 nm): ν_{max}/cm^{-1} 3325 (w), 3146 (w), 2910 (w), 2835 (w), 1686 (m), 1586 (s), 1437 (w), 1367 (w), 1331 (w), 1272 (w), 1183 (w), 1145 (w), 1121 (w), 1060 (w), 1008 (w), 938 (w), 811 (w), 776 (w), 668 (w), 626 (w), 578 (w), 540 (w), 374 (w). Mp: >132-134°C.

Synthesis of I: 4-phenyl-3-thiosemicarbazide (0.803 g, 4.8 mmol) was dissolved in de-ionised water/ethanol solution (50 mL water, 25 mL ethanol, 50 °C). Insoluble particulates were filtered off and HCl (32%, 3 drops) was added. Methylglyoxal-1,1-dimethylacetal (1.74 mL, 14.4 mmol, 1.698 g) was added rapidly and the solution was vigorously stirred at 50 °C for 5 min. The precipitate was recovered via filtration, washed with de-ionised water (2 x 50 mL) and dried. A yellow solid (0.821 g) was recovered (77% yield). δ_H 11.49 (1 H, s, N-NH), 10.57 (1 H, s, Ph-NH), 9.45 (1 H, s, O=CH), 7.53 (2 H, m, $H_{(2,6)}$ aryl), 7.36 (2 H, m, $H_{(3,5)}$ aryl), 7.20 (1 H, m, $H_{(4)}$ aryl), 1.97 (3 H, s, N=C-CH_3). δ_C 192.57 (C=O), 178.24 (C=S), 146.53 (C=N), 139.48 ($C_{(1)}$ aryl), 139.11 ($C_{(1)}$ aryl), 128.33 ($C_{(3,5)}$ aryl), 126.40 ($C_{(4)}$ aryl), 126.24 ($C_{(2,6)}$ aryl), 9.88 (N=C-CH_3). IR: ν_{max}/cm^{-1} 3277 (w), 3150 (m), 2968 (w), 2851 (w), 1697 (m), 1593 (m), 1520 (s), 1495 (s), 1447 (m), 1425 (m), 1366 (m), 1229 (m), 1167 (s), 1157 (s), 1119 (m), 1016 (m), 935 (m), 831 (m), 748 (m), 698 (s), 615 (s), 590 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3283 (w), 3068 (w), 2918 (w), 2860 (w), 1695 (s), 1590 (s), 1518 (m), 1448 (w), 1346 (w), 1292 (m), 1227 (m), 1146 (m), 1117 (m), 1030 (w), 1005 (s), 933 (w), 834 (w), 770 (w), 752 (m), 680 (w), 617 (m), 607 (m), 448 (w), 411 (w), 269 (w). Mp: >151 °C (dec.).

Synthesis of J: 4,4-dimethyl-3-thiosemicarbazide (0.500 g, 4.2 mmol) was dissolved in de-ionised water (60 mL). Solution cooled (4 °C) over ice, followed by the addition of HCl (32%, 2 drops). 2,3-butanedione (0.36 mL, 41.0 mmol, 0.35 g) was added rapidly and vigorously stirred at 5 °C for 1 h. The precipitate was recovered via filtration, washed with de-ionised water (2 x 30 mL). The crude was recrystallized from ethanol in a freezer. The crystalline solid was filtered off, washed with petroleum ether (2 x 10 mL) and left to dry. A bright yellow crystalline solid (0.191 g) was recovered (25% yield). δ_H 9.85 (1 H, s, N-NH), 3.27 (6 H, s, N-$(CH_3)_2$), 2.28 (3 H, s, O=C-CH_3), 1.91 (3 H, s, N=C-CH_3). δ_C 197.81 (C=O), 182.39 (C=S), 147.05 (C=N), 43.16 (N-$(CH_3)_2$), 24.83 (O=C-CH_3), 10.07 (N=C-CH_3). IR: ν_{max}/cm^{-1} 3362 (w), 2920 (w), 1670 (s), 1578 (m), 1537 (m), 1429 (m), 1354 (s), 1290 (s), 1198 (s), 1150 (s), 1107 (s), 1063 (s), 1005 (m), 901 (m), 804 (s), 702 (m), 611 (m), 602 (m), 527 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3364 (w), 2923 (w), 1669 (s), 1580 (s), 1364 (m), 1342 (m), 1289 (w), 1194 (m), 1150 (w), 1009 (m), 946 (w), 903 (w), 805 (w), 701 (w), 633 (w), 603 (w), 525 (w), 457 (w), 370 (w), 217 (w). Mp: >129°C (dec.).

Synthesis of K: Thiosemicarbazide (1.55 g, 17.0 mmol) was dissolved in de-ionised water (200 mL, warm). Solution cooled (10°C) over ice, followed by the addition of HCl (32%, 20 drops). 2,3-pentanedione (7.12 mL, 68 mmol, 6.81 g) was added rapidly and vigorously stirred at 10°C for 10 min. The precipitate was recovered via filtration, washed with de-ionised water (2 x 50 mL) and dried. An off white solid (1.957g) was recovered (66% yield). δ_H 10.55 (1 H, s, N-NH), 8.66 (1 H, s, C-NH), 8.04 (1 H, s, C-NH),2.90 (2H, q, J = 7.2, CH_2), 1.92 (3 H, s, N=C-CH_3), 0.90 (3 H, t, J = 7.2, C-CH_2-CH_3). δ_C 200.71 (C=O), 180.25 (C=S), 145.90 (C=N), 29.64 (C-CH_2), 10.88 (N=C-CH_3), 8.68 (C-CH_2-CH_3). IR: ν_{max}/cm^{-1} 3412 (w), 3302 (m), 3177 (m), 2984 (w), 1688 (s), 1593 (s), 1491 (m), 1422 (m), 1362 (m), 1233 (s), 1090 (s), 1043 (s), 932 (m), 843 (m), 797 (m), 700 (m), 590 (s), 552 (s). Raman (632.81

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nm): ν_{max}/cm^{-1} 3302 (w), 3192 (w), 2986 (w), 2945 (w), 2919 (w), 2898 (w), 1683 (m), 1614 (s), 1464 (w), 1364 (w), 1258 (w), 1103 (m), 1091 (m), 1045 (m), 930 (w), 838 (w), 602 (w), 487 (w), 461 (w), 410 (w), 313 (w). Mp: >165 ^{o}C (dec.).

Synthesis of L: 4-methyl-3-thiosemicarbazide (1.788 g, 17.0 mmol) was dissolved in a solution of de-ionised water (200 mL) and ethanol (80 mL). The solution was cooled (-10^{o}C) in a salt/ice bath (300 g ice, 100 g table salt), followed by the addition of HCl (32%, 6 drops). 2,3-pentanedione (3.56 mL, 34 mmol, 3.41 g) was added rapidly and vigorously stirred at *ca.* -10^{o}C for 5 m. The precipitate was recovered via filtration, washed with de-ionised water (4 x 50 mL) and dried. An off white solid (1.572g) was recovered (49% yield). δ_H 10.58 (1 H, s, N-NH), 8.55 (1 H, q, J =4.8, H_3C-N*H*), 3.00 (3 H, d, J = 4.8, HN-C*H*$_3$), 2.93 (2H, q, J = 7.2, C-CH$_2$), 1.93 (3 H, s, N=C-CH$_3$), 0.93 (3 H, t, J = 7.2, CH$_2$-C*H*$_3$). δ_C 200.54 (C=O), 179.48 (C=S), 145.60 (C=N), 31.91 (HN-CH$_3$), 29.59 (C-*C*H$_2$), 10.84 (N=C-*C*H$_3$), 8.62 (CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3379 (w), 3210 (w), 2982 (w), 1682 (s), 1541 (s), 1499 (s), 1429 (m), 1406 (m), 1375 (m), 1360 (m), 1207 (s), 1146 (s), 1107 (s), 1088 (s), 1055 (m), 1034 (s), 932 (m), 835 (m), 797 (m), 652 (m), 559 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3322 (w), 2940 (w), 1684 (m), 1677 (m), 1600 (s), 1367 (w), 1203 (m), 1143 (w), 1115 (w), 1090 (w), 1047 (m), 831 (m), 649 (w), 561 (w), 415 (w), 315 (w). Mp: >136-141 ^{o}C.

Synthesis of M: 4-ethyl-3-thiosemicarbazide (1.013 g, 85.0 mmol) dissolved in a solution of de-ionised water (100 mL) and ethanol (60 mL). The solution was cooled (-12^{o}C) in a salt/ice bath (300 g ice, 100 g table salt), followed by the addition of HCl (32%, 3 drops). 2,3-pentanedione (1.78 mL, 17 mmol, 1.70 g) was added rapidly and vigorously stirred at *ca.* -11^{o}C for 4 m. The precipitate was recovered via filtration, washed with de-ionised water (3 x 50 mL) and dried. An off white solid (0.862g) was recovered (50% yield). δ_H 10.51 (1 H, s, N-NH), 8.60 (1 H, t, J = 6.0, H_2C-N*H*), 3.58 (2 H, dq, J = 7.6, 6.0, HN-C*H*$_2$), 2.93 (2H, q, J = 7.2, C-CH$_2$), 1.93 (3 H, s, N=C-CH$_3$), 1.11 (3 H, t, J = 7.6, N-CH$_2$-C*H*$_3$), 0.93 (3 H, t, J = 7.2, C-CH$_2$-C*H*$_3$). δ_C 200.53 (C=O), 178.47 (C=S), 145.65 (C=N), 39.27 (HN-CH$_2$), 29.59 (C-*C*H$_2$), 14.66 (N-CH$_2$-*C*H$_3$), 10.86 (N=C-*C*H$_3$), 8.60 (C-CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3345 (w), 3188 (w), 2974 (w), 1686 (s), 1612 (w), 1537 (s), 1499 (s), 1427 (m), 1364 (m), 1190 (s), 1155 (m), 1117 (m), 1092 (m), 1038 (s), 949 (m), 824 (m), 800 (m), 600 (s), 563 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3346 (w), 2913 (w), 1683 (w), 1611 (w), 1448 (w), 1366 (w), 1265 (w), 1189 (w), 1153 (w), 1115 (w), 1039 (w), 819 (w), 654 (w), 560 (w), 304 (w). Mp: >103-104 ^{o}C.

Proligands 1 - 30

Known proligands **1**,[22] **2**,[33] **5**,[22] **20**,[22] **21**,[58] **22**[30] and **25**[22] were synthesised as described previously. Previously reported proligands **6**, **7**, and **8** were synthesised by new methods described below. Other previously reported proligands listed in Table 2 were not synthesised in this work and their data reported in Table 2 are literature values.

Synthesis of 3: Compound **B** (0.510 g, 0.0032 mol) was dissolved in DMF (3 mL) and filtered. Thiosemicarbazide (0.292 g, 0.0032 mol) was dissolved in DMF (10 mL), HCl (10%, 2 drops) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (26 mL) was added, the precipitate was filtered off and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C). The crude product was dissolved in DMSO (10 mL) the resulting solution was filtered and recrystallised with de-ionised water (20 mL). The precipitate was recovered via filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C) and dried. A white solid (0.456 g) was recovered (61% yield). δ_H 11.66 (s, 1 H, N-

N*H*), 10.35 (s, 1 H, N-N*H*), 8.50 (q, 1 H, H_3C-N*H*, J= 4.8 Hz), 8.28 (s, 1 H C-N*H*), 7.87 (s, 1 H C-N*H*), 7.61 (s, 1 H, N=C*H*), 2.94 (d, 3 H, HN-CH_3, J= 4.8 Hz), 2.09 (s, 3 H, N=C-CH_3). δ_C 178.76 (*C*=S), 178.59 (*C*=S), 147.54 (*C*=N), 142.95 (*C*=N), 31.58 (HN-*C*H_3), 11.52 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3414 (w), 3148 (m), 1988 (w), 1607 (m), 1531 (s), 1497 (s), 1458 (m), 1364 (m), 1335 (m), 1269 (m), 1217 (s), 1155 (m), 1070 (s), 924 (m), 833 (s), 656 (m), 565 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2915 (w), 1672 (w), 1600 (m), 1585 (s), 1374 (w), 1336 (w), 1268 (w), 1223 (w), 1126 (w), 1013 (w), 878 (w), 792 (w), 481 (w), 307 (w), 219 (w). Found: C, 31.1; H, 5.1; N, 36.1. Calc. for $C_6H_{12}N_6S_2$: C, 31.0; H, 5.1; N, 36.2%. Mp: >217 ^{o}C (dec.).

Synthesis of 4: Freshly activated molecular sieves (3 Å, 0.075 g) was added to DMF (17 mL, 60 ^{o}C), followed by the addition of compound **D** (0.131 g, 0.0009 mol) and 4-methyl-3-thiosemicarbazide (0.101 g, 0.0010 mol). The heat was turned off and the solution was left to stir (3 days, cooling down to room temperature). The molecular sieves were filtered off and the DMF was removed under vacuum. The crude product was washed with a little ethyl acetate and diethyl ether (1 x 25 mL) and dried. A sawdust coloured solid (0.130 g) was recovered (62% yield). δ_H 11.69 (s, 1 H, N-N*H*), 10.33 (s, 1 H, N-N*H*), 8.38 (quartet overlapping a singlet, 1 H, H_3C-N*H*, J= 4.4 Hz), 8.35 (singlet overlapping a quartet, 1 H C-N*H*), 7.60 (s, 1 H C-N*H*), 7.61 (s, 1 H, N=C*H*), 2.95 (d, 3 H, HN-CH_3, J= 4.4 Hz), 2.04 (s, 3 H, N=C-CH_3). δ_C 179.27 (*C*=S), 178.24 (*C*=S), 148.02 (*C*=N), 142.55 (*C*=N), 31.47 (HN-*C*H_3), 11.62 (N=C-*C*H_3).

Synthesis of 5: 4-methyl-3-thiosemicarbazide (1.100 g, 0.0105 mol) was dissolved in de-ionised water (40 mL, 50 ^{o}C) and HCl (32%, 2 drops) was added. Methylglyoxal-1,1-dimethylacetal (0.58 mL, 0.0048 mol, 0.566 g) was added rapidly and left to stir (50 ^{o}C, 5 minutes). The precipitate was removed by filtration and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C). The crude product was dissolved in DMSO (17 mL). The solution was filtered, recrystallised with de-ionised water (34 mL). The precipitate was removed via filtration, washed with water (50 mL) and left to dry. A cream solid (0.858 g) was recovered (73% yield). δ_H 11.73 (s, 1 H, N-N*H*), 10.33 (s, 1 H, N-N*H*), 8.49 (m, 1 H, H_3C-N*H*, J= 4.4 Hz), 8.38 (m, 1 H H_3C-N*H*, J= 4.8 Hz), 7.62 (s, 1 H, N=C*H*), 2.94 (two over lapping doublets, 6 H, HN-CH_3, J= 4.4 Hz), 2.12 (s, 3 H, N=C-CH_3). δ_C 178.76 (*C*=S), 178.22 (*C*=S), 147.63 (*C*=N), 142.40 (*C*=N), 31.58 (HN-*C*H_3), 31.47 (HN-*C*H_3), 11.62 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3302 (w), 3142 (w), 1531 (s), 1489 (s), 1431 (m), 1408 (m), 1354 (w), 1213 (s), 1152 (m), 1088 (s), 1024 (s), 914 (m), 820 (m), 548 (s), 517 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 2909 (w), 1785 (w), 1657 (w), 1577 (s), 1442 (w), 1364 (w), 1279 (w), 1226 (w), 1124 (w), 1017 (w), 879 (w), 775 (w), 560 (w), 405 (w), 115 (w). Mp: >214 ^{o}C (dec.).

Synthesis of 6: 4,4-dimethyl-3-thiosemicarbazide (0.321 g, 0.0027 mol) was dissolved in de-ionised water (50 mL, 50 ^{o}C) and HCl (32%, 2 drops) was added. Methylglyoxal-1,1-dimethylacetal (0.15 mL, 0.0012 mol, 0.15 g) was added rapidly and left to stir (50 ^{o}C, 1 hour). The precipitate was removed by filtration and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C). The crude product was dissolved in DMSO (3 mL). The solution was filtered, and the product was recrystallised with de-ionised water (6 mL). The precipitate was recovered by filtration, washed with water (50 mL) and dried. A yellow solid (0.065 g) was recovered (20% yield). δ_H 11.07 (s, 1 H, N-N*H*), 9.59 (s, 1 H, N-N*H*), 7.78 (s, 1 H, N=C*H*), 3.23 (s, 6 H, N-(CH_3)$_2$), 2.05 (s, 3 H, N=C-CH_3). δ_C 181.79 (*C*=S), 180.89 (*C*=S), 150.11 (*C*=N), 144.54 (*C*=N), 42.80 (N-(*C*H_3)$_2$), 42.47 (N-(*C*H_3)$_2$), 11.37 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3404 (w), 2922 (w), 1533 (s), 1490 (m), 1362 (m), 1328 (s), 1281 (m), 1229 (s), 1150 (s), 1113 (m), 1057 (m), 1022 (m), 905 (s), 785 (m), 542 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 2917 (w), 1581 (s), 1436 (w),

1381 (w), 1281 (w), 1237 (m), 1132 (w), 1027 (w), 864 (w), 718 (w), 546 (w), 438 (w), 394 (w), 171 (w), 107 (w). Mp. >106 °C (dec.).

Synthesis of 7: 4-ethyl-3-thiosemicarbazide (1.251 g, 0.0105 mol) was dissolved in de-ionised water (50 mL, 50 °C). The insoluble particulates were filtered and HCl was added (32%, 2 drops). Methylglyoxal-1,1-dimethylacetal (0.58 mL, 0.0048 mol, 0.57 g) was added rapidly and left to stir (50 °C, 5 minutes). The precipitate was removed by filtration and washed with de-ionised water (50 mL). The crude product was dissolved in DMSO (35 mL). The solution was filtered and the product was recrystallised with de-ionised water (70 mL). The precipitate was isolated via filtration, washed with water (50 mL) and dried. A yellowish white solid (0.870 g) was recovered (66% yield). δ_H 11.65 (s, 1 H, N-N*H*), 10.24 (s, 1 H, N-N*H*), 8.52 (t, 1 H, H_2C-N*H*, J= 6.0 Hz), 8.41 (t, 1 H H_2C-N*H*, J= 6.0 Hz), 7.62 (s, 1 H, N=C*H*), 3.52 (m, 4 H, *H_2*C-NH), 2.13 (s, 3 H, N=C-C*H_3*), 1.07 (two overlapping triplets, 6 H, H_2C-C*H_3*, J= 7.2 Hz). δ_C 177.65 (*C*=S), 177.15 (*C*=S), 147.66 (*C*=N), 142.41 (*C*=N), 39.01 (N-*C*H_2), 38.87 (N-*C*H_2), 15.01 (H_2C-*C*H_3), 14.87 (H_2C-*C*H_3), 11.38 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3289 (m), 3161 (w), 2967 (m), 1526 (s), 1476 (s), 1427 (s), 1315 (m), 1229 (s), 1198 (s), 1096 (s), 1043 (s), 934 (s), 808 (s), 664 (m), 579 (s), 550 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3375 (w), 2936 (w), 1578 (s), 1516 (w), 1436 (w), 1365 (m), 1284 (w), 1236 (w), 1202 (w), 1132 (w), 1020 (w), 874 (w), 757 (w), 541 (w), 457 (w). Mp. >220 °C (dec.).

Synthesis of 8: 4-phenyl-3-thiosemicarbazide (0.439 g, 2.63mmol) was dissolved in de-ionised water/ethanol solution (25 mL water, 13 mL ethanol, 50 °C). The insoluble particulates were filtered and HCl (32%, 2 drops) was added. Methylgloxal-1,1-dimethylacetal (0.15 mL, 1.2 mmol, 0.146 g) was added rapidly and left to stir at 50 °C for 5 min. The precipitate was removed by filtration and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (15 mL). The solution was filtered, the product was recrystallised with de-ionised water (30 mL). The precipitate was filtered and washed with water (50 mL) and dried. The sample was further washed with ethanol (2 x 25 mL), de-ionised water (50 mL, 80 °C) and dried. A mustard coloured solid (0.244 g) was recovered (55% yield). δ_H 12.10 (1 H, s, N-NH), 10.75 (1 H, s, N-NH), 10.19 (1 H, s, Ph-NH), 10.01 (1 H, s, Ph-NH), 7.82 (1 H, s, N=CH), 7.50 (4 H, m, $H_{(2,6)}$ aryl), 7.32 (4 H, m, $H_{(3,5)}$ aryl), 7.17 (2 H, m, $H_{(4)}$ aryl), 2.25 (3 H, s, N=C-CH_3). δ_C 177.30 (C=S), 176.76 (C=S), 148.49 (C=N), 143.48 (C=N), 139.48 ($C_{(1)}$ aryl), 139.45 ($C_{(1)}$ aryl), 128.66 ($C_{(3,5)}$ aryl), 126.55 ($C_{(4)}$ aryl), 126.09 ($C_{(2,6)}$ aryl), 11.97 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3292 (w), 3136 (w), 2980 (w), 1595 (m), 1518 (s), 1491 (s), 1445 (m), 1350 (m), 1256 (m), 1173 (s), 1070 (m), 1026 (m), 934 (m), 750 (m), 689 (s), 640 (m), 559 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 3061 (w), 1579 (s), 1433 (w), 1370 (w), 1285 (w), 1254 (m), 1178 (w), 1122 (w), 1023 (w), 942 (w), 1864 (w), 744 (w), 614 (w), 257 (w), 195 (w). Mp: >177 °C (dec.).

Synthesis of 9: Compound **B** (0.255 g, 0.0016 mol) was dissolved in DMF (1.5 mL) and filtered. 4,4-dimethyl-3-thiosemicarbazide (0.191 g, 0.0016 mol) was dissolved in DMF (3 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (9 mL) was added, the precipitate was filtered off and washed with de-ionised water (50 mL, room temperature and 50 mL, 80°C). The crude product was dissolved in DMSO (9 mL), filtered and recrystallised with de-ionised water (18 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL) and dried. A yellow solid (0.158 g) was recovered (38% yield). δ_H 11.19 (s, 1 H, N-N*H*), 10.41 (s, 1 H, N-N*H*), 8.45 (q, 1 H, H_3C-N*H*, J= 4.4 Hz), 7.72 (s, 1 H, N=C*H*), 3.21 (s, 6 H, HN-(C*H_3*)$_2$), 2.95 (d, 3 H, HN-C*H_3*, J= 4.4 Hz), 2.05 (s, 3 H, N=C-C*H_3*). δ_C 181.06 (*C*=S), 178.82 (*C*=S), 147.56 (*C*=N), 143.95 (*C*=N), 42.96 (N-(*C*H_3)$_2$), 31.56 (HN-*C*H_3), 11.65

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(N=C-CH_3). IR: ν_{max}/cm^{-1} 3306 (m), 3200 (m), 2999 (w), 1589 (w), 1526 (s), 1495 (s), 1406 (m), 1354 (m), 1273 (s), 1225 (s), 1142 (m), 1107 (s), 1045 (s), 966 (m), 935 (s), 878 (m), 812 (m), 658 (m), 623 (s), 584 (s), 565 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1589 (m), 1570 (s), 1417 (m), 1363 (m), 1295 (m), 1275 (m), 1225 (m), 1143 (m), 1064 (m), 1016 (m), 876 (m), 744 (m), 583 (w), 314 (w), 131 (w). Elemental analysis: Found: C, 37.0; H, 6.2; N, 32.2. Calc. for $C_8H_{16}N_6S_2$: C, 36.9; H, 6.2; N, 32.3%. Mp. >205 °C (dec.).

Synthesis of 10: Compound **B** (0.255 g, 0.0016 mol) was dissolved in DMF (1 mL) and filtered. 4-ethyl-3-thiosemicarbazide (0.191 g, 0.0016 mol) was dissolved in DMF (5 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (12 mL) was added, the precipitate was filtered and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (6 mL), filtered and recrystallised with de-ionised water (12 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL) and dried. A cream solid (0.191 g) was recovered (46% yield). δ_H 11.68 (s, 1 H, N-N*H*), 10.33 (s, 1 H, N-N*H*), 8.50 (q, 1 H, H_3C-N*H*, J= 4.4 Hz), 8.42 (t, 1 H H_2C-N*H*, J= 6.0 Hz), 7.62 (s, 1 H, N=C*H*), 3.52 (dq, 2 H, H_2C-NH, J=7.2, 6.0 Hz),2.94 (d, 3 H, N-CH_3, J= 4.4 Hz), 2.13 (s, 3 H, N=C-CH_3), 1.08 (t , 3 H, H_2C-CH_3, J= 7.2 Hz). δ_C 178.75 (*C*=S), 177.17 (*C*=S), 147.64 (*C*=N), 142.44 (*C*=N), 38.86 (N-*C*H_2), 31.58 (N-*C*H_3), 15.01 (H_2C-*C*H_3), 11.68 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3374 (w), 3316 (w), 3165 (w), 2988 (w), 1537 (s), 1497 (s), 1435 (m), 1412 (m), 1327 (m), 1219 (s), 1159 (m), 1084 (s), 1042 (m), 935 (m), 814 (m), 664 (m), 619 (m), 546 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2902 (w), 1580 (s), 1518 (w), 1364 (w), 1284 (w), 1220 (w), 1130 (w), 1016 (w), 879 (w), 773 (w), 572 (w), 461 (w), 307 (w), 236 (w), 180 (w). Found: C, 37.0; H, 6.25; N, 32.2. Calc. for $C_8H_{16}N_6S_2$: C, 36.9; H, 6.2; N, 32.3%. Mp. >220 °C (dec.).

Synthesis of 11: Compound **H** (0.554 g, 0.0032 mol) was dissolved in DMF (2 mL) and filtered. 4-methyl-3-thiosemicarbazide (0.337 g, 0.0032 mol) was dissolved in DMF (6 mL), HCl (10%, 2 drops) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (50 mL) was added, a gelatinous precipitate was recovered by filtration and washed with de-ionised water (50 mL, room temperature and 50 mL, 80°C). The crude product was left on the water pump until its volume decreased then dissolved in DMSO (6 mL), filtered and recrystallised with de-ionised water (60 mL). The waxy gelatinous precipitate was recovered by filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C), and dried. The product was further washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C), and dried. A yellowish white solid (0.118 g) was recovered (14% yield). δ_H 11.71 (s, 1 H, N-N*H*), 10.24 (s, 1 H, N-N*H*), 8.53 (t, 1 H H_2C-N*H*, J= 6.0 Hz), 8.39 (q, 1 H, H_3C-N*H*, J= 4.4 Hz), 7.62 (s, 1 H, N=C*H*), 3.52 (dq, 2 H, H_2C-NH, J=7.2, 6.0 Hz), 2.95 (d, 3 H, N-CH_3, J= 4.4 Hz), 2.12 (s, 3 H, N=C-CH_3), 1.07 (t , 3 H, H_2C-CH_3, J= 7.2 Hz). δ_C 178.23 (*C*=S), 177.69 (*C*=S), 147.70 (*C*=N), 142.37 (*C*=N), 39.00 (N-*C*H_2), 31.47 (N-*C*H_3), 14.87 (H_2C-*C*H_3), 11.62 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3366 (w), 3129 (w), 2982 (w), 1518 (s), 1491 (s), 1425 (m), 1364 (m), 1242 (m), 1204 (s), 1076 (s), 1040 (m), 914 (m), 812 (m), 631 (m), 600 (m), 540 (s), Raman (632.81 nm): ν_{max}/cm^{-1} 1581 (s), 1434 (w), 1362 (w), 1328 (w), 1275 (w), 1204 (w), 1125 (w), 1023 (w), 917 (w), 873 (w), 774 (w), 598 (w), 420 (w), 298 (w), 211 (w). Found: C, 37.0; H, 6.3; N, 32.2. Calc. for $C_8H_{16}N_6S_2$: C, 36.9; H, 6.2; N, 32.3%. Mp. >220 °C (dec.).

Synthesis of 12: Intermediate **B** (0.255 g, 1.6 mmol) was dissolved in DMF (2 mL) and filtered. 4-phenyl-3-thiosemicarbazide (0.268 g, 1.6 mol) was dissolved in DMF (2.5 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir for 5 h. De-ionised water (9 mL)

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was added, the precipitate was filtered and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (12 mL), filtered and recrystallised with de-ionised water (24 mL). The precipitate was recovered by filtration, washed with ethanol (2 x 25mL, room temperature), de-ionised water (50 mL, 80 °C) and dried. An off white solid (0.313 g) was recovered (63% yield). δ_H 12.06 (1 H, s, N-NH), 10.40 (1 H, s, N-NH), 9.97 (1 H, s, Ph-NH), 8.55 (1 H, q, J = 4.4, CH_3-N*H*), 7.73 (1 H, s, N=CH), 7.48 (2 H, d, J = 8.0, $H_{(2,6)}$ aryl), 7.33 (2 H, dd,J = 8.0, $H_{(3,5)}$ aryl), 7.17 (1 H, dd, J = 8.0, $H_{(4)}$ aryl), 2.96 (3 H, d, J = 4.4, N-CH_3), 2.18 (3 H, s, N=C-CH_3). δ_C 178.79 (C=S), 176.68 (C=S), 147.50 (C=N), 143.50 (C=N), 139.44 ($C_{(1)}$ aryl), 128.63 ($C_{(3,5)}$ aryl), 126.53 ($C_{(4)}$ aryl), 126.06 ($C_{(2,6)}$ aryl), 31.61 (N-CH_3), 11.71 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3331 (w), 3285 (w), 3136 (w), 2988 (w), 1589 (w), 1541 (s), 1499 (s), 1449 (m), 1400 (m), 1356 (m), 1315 (m), 1263 (m), 1200 (s), 1072 (s), 934 (m), 745 (m), 691 (m), 665 (m), 635 (m), 569 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3044 (w), 1585 (s), 1513 (w), 1367 (w), 1278 (w), 1236 (w), 1118 (w), 1016 (w), 934 (w), 873 (w), 745 (w), 638 (w), 410 (w), 290 (w), 224 (w). Found: C, 46.7; H, 5.2; N, 27.25. Calc. for $C_{12}H_{16}N_6S_2$: C, 46.7; H, 5.1; N, 27.2%. Mp: >205 °C (dec.).

Synthesis of 13: Compound **H** (0.554 g, 0.0032 mol) was dissolved in DMF (2 mL) and filtered. Thiosemicarbazide (0.292 g, 0.0032 mol) was dissolved in DMF (10 mL), HCl (10%, 2 drops) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (24 mL) was added, the precipitate was filtered off and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (25 mL), filtered and recrystallised with de-ionised water (50 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C), and dried. An off white solid (0.386 g) was recovered (49% yield). δ_H 11.65 (1 H, s, N-NH), 10.26 (1 H, s, N-NH), 8.53 (1 H, t, J = 6.0, H_2C-N*H*), 8.28 (1 H, s, C-NH), 7.88 (1 H, s, C-NH), 7.62 (1 H, s, N=CH), 3.52 (2 H, dq, J = 7.2, 6.0, *H*$_2$C-NH), 2.09 (3 H, s, N=C-CH_3), 1.07 (3 H, t, J = 7.2, H_2C-C*H*$_3$). δ_C 178.57 (C=S), 177.67 (C=S), 147.62 (C=N), 142.93 (C=N), 38.99 (N-CH_2), 14.87 (H_2C-*C*H_3), 11.53 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3292 (w), 3148 (m), 2982 (m), 1593 (m), 1530 (s), 1493 (s), 1456 (m), 1352 (m), 1310 (m), 1269 (m), 1202 (s), 1090 (s), 926 (m), 829 (s), 662 (m), 548 (s). Raman(632.81 nm): ν_{max}/cm^{-1} 2978 (w), 2908 (w), 1583 (s), 1425 (w), 1350 (w), 1270 (w), 1209 (w), 1128 (w), 1014 (w), 936 (w), 874 (w), 800 (w), 483 (w), 307 (w), 209 (w). Found: C, 34.0; H, 5.8; N, 34.0. Calc. for $C_7H_{14}N_6S_2$: C, 34.1; H, 5.7; N, 34.1%. Mp: >207 °C (dec.).

Synthesis of 14: Compound **H** (0.277 g, 0.0016 mol) was dissolved in DMF (1.5 mL) and filtered. 4,4-dimethyl-3-thiosemicarbazide (0.191 g, 0.0016 mol) was dissolved in DMF (3 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (24 mL) was added, the precipitate was filtered and washed with de-ionised water (2 x 50 mL). The crude product was dissolved in DMSO (7 mL), filtered and recrystallised with de-ionised water (14 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL, 80 °C) and dried. A yellow solid (0.117 g) was recovered (27% yield). δ_H 11.18 (1 H, s, N-NH), 10.36 (1 H, s, N-NH), 8.46 (1 H, t, J = 6.0, H_2C-N*H*), 7.75 (1 H, s, N=CH), 3.52 (2 H, dq, J =7.2, 6.0, *H*$_2$C-NH), 3.21 (6 H, s, HN-(C*H*$_3$)$_2$), 2.05 (3 H, s, N=C-CH_3), 1.08 (3 H, t, J = 7.2, H_2C-C*H*$_3$). δ_C 181.00 (C=S), 177.76 (C=S), 147.57 (C=N), 144.09 (C=N), 42.90 (HN-(CH_3)$_2$), 39.00 (N-CH_2), 14.87 (H_2C-*C*H_3), 11.67 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3341 (w), 3134 (m), 2988 (m), 1589 (w), 1526 (s), 1489 (s), 1410 (m), 1348 (m), 1269 (s), 1206 (s), 1140 (m), 1049 (s), 920 (s), 868 (m), 806 (m), 783 (m), 660 (m), 625 (m), 581 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 2936 (w), 1575 (s), 1361 (w), 1284 (w), 1274

(w), 1206 (w), 1143 (w), 1102 (w), 1016 (w), 964 (w), 934 (w), 870 (w), 742 (w), 626 (w), 308 (w). Found: C, 39.4; H, 6.7; N, 30.6. Calc. for $C_9H_{18}N_6S_2$: C, 39.4; H, 6.6; N, 30.6%. Mp: >180 ^{o}C (dec.).

Synthesis of 15: Compound **15** was prepared from compound H and 4-phenyl-3-thiosemicarbazide in a similar manner to **14** above. ^{1}H NMR showed that the product was contaminated with up to 10% of the (known[22]) symmetric ligand **8**.

Synthesis of 16: Compound **I** (0.354 g, 0.0016 mol) was dissolved in DMF (2.5 mL) and filtered. Thiosemicarbazide (0.146 g, 0.0016 mol) was dissolved in DMF (5 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (15 mL) was added, the precipitate was filtered and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C). The crude product was dissolved in DMSO (7 mL), filtered and recrystallised with de-ionised water (14 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C), and dried. A yellowish white solid (0.273 g) was recovered (58% yield). δ_H 11.70 (1 H, s, N-NH), 10.71 (1 H, s, N-NH), 10.15 (1 H, s, Ph-NH), 8.32 (1 H, s, C-NH), 7.92 (1 H, s, C-NH), 7.71 (1 H, s, N=CH), 7.50 (2 H, d, J= 8.0, $H_{(2,6)}$ aryl), 7.31 (2 H, dd, J = 8.0, $H_{(3,5)}$ aryl), 7.15 (1 H, dd, J = 8.0, $H_{(4)}$ aryl), 2.16 (3 H, s, N=C-CH_3). δ_C 178.71 (C=S), 177.27 (C=S), 148.54 (C=N), 142.93 (C=N), 139.48 ($C_{(1)}$ aryl), 128.64 ($C_{(3,5)}$ aryl), 126.09 ($C_{(4)}$ aryl), 125.91 ($C_{(2,6)}$ aryl), 11.77 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3449 (w), 3296 (w), 3157 (m), 2974 (w), 1595 (m), 1516 (s), 1493 (s), 1447 (m), 1366 (m), 1335 (m), 1267 (m), 1250 (m), 1179 (s), 1090 (s), 1069 (m), 1024 (m), 935 (m), 824 (m), 756 (m), 694 (s), 588 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3054 (w), 1580 (w), 1373 (w), 1277 (w), 1253 (w), 1172 (w), 1124 (w), 1017 (w), 937 (w), 870 (w), 781 (w), 758 (w), 608 (w), 423 (w), 259 (w), 206 (w). Found: C, 44.7; H, 4.8; N, 28.5. Calc. for $C_{11}H_{14}N_6S_2$: C, 44.9; H, 4.8; N, 27.2%. Mp: >215 ^{o}C (dec.).

Synthesis of 17: Compound **I** (0.354 g, 0.0016 mol) was dissolved in DMF (2.5 mL) and filtered. 4-methyl-3-thiosemicarbazide (0.168 g, 0.0016 mol) was dissolved in DMF (4 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (13 mL) was added, the precipitate was filtered and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C). The crude product was dissolved in DMSO (10 mL), filtered and recrystallised with de-ionised water (20 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 ^{o}C), and dried. An off-white solid (0.319 g) was recovered (65% yield). δ_H 11.77 (1 H, s, N-NH), 10.70 (1 H, s, N-NH), 10.14 (1 H, s, Ph-NH), 8.43 (1 H, q, J = 4.4, H_3C-N*H*), 7.71 (1 H, s, N=CH), 7.50 (2 H, d, J = 8.0, $H_{(2,6)}$ aryl), 7.31 (2 H, dd, J = 8.0, $H_{(3,5)}$ aryl), 7.15 (1 H, dd, J = 8.0, $H_{(4)}$ aryl), 2.96 (3 H, d, J = 4.4, N-CH_3), 2.20 (3 H, s, N=C-CH_3). δ_C 178.29 (C=S), 177.23 (C=S), 148.63 (C=N), 142.39 (C=N), 139.48 ($C_{(1)}$ aryl), 128.64 ($C_{(3,5)}$ aryl), 126.06 ($C_{(4)}$ aryl), 125.89 ($C_{(2,6)}$ aryl), 31.49 (N-CH_3), 11.87 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3291 (w), 3157 (w), 2999 (w), 1595 (w), 1518 (s), 1495 (s), 1477 (s), 1447 (m), 1352 (m), 1250 (m), 1173 (s), 1090 (m), 1038 (m), 932 (m), 797 (m), 748 (m), 687 (m), 559 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1577 (s), 1514 (w), 1367 (w), 1286 (w), 1247 (w), 1174 (w), 1128 (w), 1020 (w), 934 (w), 874 (w), 773 (w), 602 (w), 541 (w), 435 (w), 194 (w). Found: C, 46.7; H, 5.2; N, 27.25. Calc. for $C_{12}H_{16}N_6S_2$: C, 46.6; H, 5.2; N, 27.6%. Mp: >210 ^{o}C (dec.).

Synthesis of 18: Proligand **18** was synthesised fro compound H and 4,4-dimethyl-3-thiosemicarbazide in a similar manner to **14** above, but ^{1}H NMR indicated that the product was contaminated with up to 25% of the (known[22]) pro-ligand **8**.

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Synthesis of 19: Compound **I** (0.354 g, 0.0016 mol) was dissolved in DMF (2.5 mL) and filtered. 4-ethyl-3-thiosemicarbazide (0.191 g, 0.0016 mol) was dissolved in DMF (5 mL), HCl (10%, 1 drop) was added and filtered. The two solutions were combined and left to stir (room temperature, 5 hours). De-ionised water (15 mL) was added, the precipitate was filtered and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (11 mL), filtered and recrystallised with de-ionised water (22 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C), and dried. A yellowish cream solid (0.309 g) was recovered (60% yield). δ_H 11.71 (1 H, s, N-NH), 10.69 (1 H, s, N-NH), 10.15 (1 H, s, Ph-NH), 8.47 (1 H, t, J = 6.0, H_2C-N*H*), 7.71 (1 H, s, N=CH), 7.50 (2 H, d, J = 8.0, $H_{(2,6)}$ aryl), 7.32 (2 H, dd, J = 8.0, $H_{(3,5)}$ aryl), 7.15 (1 H, dd, J =8.0, $H_{(4)}$ aryl), 3.54 (2 H, dq, J = 7.2, 6.0, *H*$_2$C-NH), 2.21 (3 H, s, N=C-CH_3), 1.09 (3 H, t, J = 7.2, H_2C-C*H*$_3$). δ_C 177.24 (C=S), 148.63 (C=N), 142.42 (C=N), 139.48 ($C_{(1)}$ aryl), 128.64 ($C_{(3,5)}$ aryl), 126.06 ($C_{(4)}$ aryl), 125.90 ($C_{(2,6)}$ aryl), 38.90 (N-CH_2), 15.00 (H_2C-*C*H_3), 11.93 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3294 (w), 3132 (m), 2970 (w), 1591 (w), 1518 (s), 1491 (s), 1447 (m), 1335 (m), 1277 (m), 1227 (s), 1182 (s), 1123 (m), 1072 (m), 937 (m), 787 (m), 748 (m), 696 (s), 635 (m), 577 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2966 (w), 1582 (s), 1445 (w), 1372 (w), 1253 (w), 1177 (m), 1125 (w), 1019 (w), 924 (w), 865 (w), 751 (w), 527 (w), 419 (w), 293 (w), 206 (w). Found: C, 48.3; H, 5.6; N, 26.0. Calc. for $C_{13}H_{18}N_6S_2$: C, 48.4; H, 5.6; N, 26.0%. Mp: >207 °C (dec.).

Synthesis of 23: **Method 1:** Thiosemicarbazide (0.158 g, 1.7 mmol) was dissolved in ethanol (50 mL, 50 °C) and added HCl (10%, 1 drop). Compound **F** (0.300 g, 1.7 mmol) added to the solution and left to stir at 50 °C for 5 h. The precipitate was recovered by filtration, dissolved in DMSO (5 mL) and recrystallised with de-ionised water (5 mL). The precipitate was filtered off, washed with a little amount of acetone and dried. A white solid (0.145 g) was recovered (35% yield). δ_H 10.19 (2 H, s, N-NH), 8.37 (1 H, s, C-NH), 8.34 (1 H, q, J = 4.4, H_3C-N*H*), 7.82 (1 H, s, C-NH), 2.97 (3 H, d, J = 4.4, HN-C*H*$_3$), 2.16 (3 H, s, N=C-CH_3), 2.12 (3 H, s, N=C-CH_3). δ_C 179.32 (C=S), 178.97 (C=S), 148.92 (C=N), 148.43 (C=N), 31.74 (HN-CH_3), 12.26 (N=C-*C*H_3), 12.07 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3414 (m), 3352 (w), 3215 (m), 3150 (m), 1605 (m), 1553 (m), 1489 (s), 1362 (m), 1288 (m), 1231 (m), 1169 (m), 1142 (m), 1080 (s), 953 (m), 854 (m), 826 (m), 716 (m), 644 (m), 565 (s), 544 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3212 (w), 2913 (w), 1604 (s), 1589 (m), 1461 (w), 1374 (m), 1329 (w), 1237 (w), 1123 (w), 1005 (w), 854 (w), 747 (w), 461 (w), 398 (w), 216 (w). Found: C, 34.2; H, 5.8; N, 34.0. Calc. for $C_7H_{14}N_6S_2$: C, 34.1; H, 5.7; N, 34.1%. Mp: >215 °C (dec.). **Method 2:** 2,3-butanedione (5.26 mL, 60 mmols) was dissolved in 100 mL of cold distilled water (0 °C) in a conical flask. Five drops of concentrated HCl (97%) were added to the reaction mixture, followed by 4-methyl-3-thiosemicarbazide (3.45 g, 32.8 mmol). After stirring for 1 hour, the resulting suspension was filtered and the residue rinsed with water (3 x 100 mL), ethanol (3 x 50 mL) and diethyl ether (3 x 10 mL) and recrystallised from warm ethanol to afford pure mono-substituted-3-thiosemicarbazone intermediate (2.4 g, 43%). This intermediate (0.80 g, 4.62 mmols) was added over 2 h in portions to a solution of thiosemicarbazide in methanol (0.44 g, 4.82 mmol) previously acidified with concentrated HCl. The reaction mixture was heated under reflux (~65 °C) for 5 h, during which a whitish suspension formed. After cooling down to room temperature, the solution was filtered under vacuum and the precipitate washed with ethanol (3 x 50 mL) and diethyl ether (3 x 10 mL). The resulting solid was then recrystallised from warm DMSO/water (50:50) to yield pure **23** (0.90 g, 79%).

Synthesis of 24: Intermediate **G** (0.255 g, 1.6 mmol) was dissolved in DMF (1.5 mL) and filtered. 4,4-dimethyl-3-thiosemicarbazide (0.191 g, 1.6 mmol) dissolved in DMF (2.5 mL), HCl (10%, 2 drops) was added and filtered. The two solutions were combined and left to stir for 5 h. De-ionised water (33

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mL) was added, the precipitate was recovered by filtration and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (3 mL), filtered and recrystallised with de-ionised water (6 mL). The precipitate was filtered off, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C) and dried. A yellow solid (0.170 g) was recovered (41% yield). δ_H 10.18 (1 H, s, N-NH), 9.49 (1 H, s, N-N***H***), 8.38 (1 H, s, C-NH), 7.83 (1 H, s, C-NH), 3.22 (6 H, s, N-$(CH_3)_2$), 2.11 (3 H, s, N=C-CH_3), 2.10 (3 H, s, N=C-CH_3). δ_C 182.16 (C=S), 179.35 (C=S), 150.00 (C=N), 148.96 (C=N), 42.80 (N-$(CH_3)_2$), 11.96 (N=C-*C*H_3), 11.70 (N=C-*C*H_3). IR: ν_{max}/cm^{-1} 3395 (w), 3221 (m), 3148 (m), 1591 (m), 1545 (m), 1460 (m), 1412 (m), 1396 (m), 1368 (m), 1261 (m), 1221 (m), 1134 (m), 1103 (m), 1055 (m), 968 (m), 847 (m), 708 (m), 606 (m), 515 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2913 (w), 1603 (m), 1586 (s), 1498 (w), 1463 (w), 1397 (w), 1371 (w), 1338 (m), 1263 (w), 1229 (w), 1128 (m), 1110 (w), 1006 (w), 850 (w), 736 (w), 612 (w), 461 (w).Found: C, 36.9; H, 6.2; N, 32.3. Calc. for $C_8H_{16}N_6S_2$: C, 36.9; H, 6.2; N, 32.2%. Mp: >192 °C (dec.).

Synthesis of 26: Intermediate **K** (0.277 g, 1.6 mmol) was dissolved in DMF (3 mL). 4-methyl-3-thiosemicarbazide (0.168 g, 1.6 mmol) was dissolved in DMF (4 mL) and HCl (10%, 1 drop) was added. The two solutions were combined and left to stir for 5 h. De-ionised water (14 mL) was added, the precipitate was filtered and washed with de-ionised water (50 mL). The crude product was dissolved in DMSO (8 mL) and recrystallised with de-ionised water (16 mL). The precipitate was filtered off, washed with de-ionised water (50 mL), ethanol (5 x 10 mL) and dried. A yellow/white solid (0.275 g) was recovered (66% yield). δ_H10.37 (1 H, s, N-NH), 10.19 (1 H, s, N-NH), 8.40 (1 H, s, C-NH), 8.32 (1 H, q, J =4.8, H_3C-N*H*), 7.74 (1 H, s, C-NH), 2.97 (3 H, d, J = 4.8, HN-CH_3), 2.80 (2H, q, J = 7.6, C-CH_2), 2.10 (3 H, s, N=C-CH_3), 0.84 (3 H, t, J = 7.2, CH_2-CH_3). δ_C 179.28 (C=S), 178.93 (C=S), 152.24 (C=N), 147.92 (C=N), 31.76 (HN-CH_3), 17.38 (C-*C*H_2), 12.38 (N=C-*C*H_3), 11.45 (CH_2-*C*H_3). IR: ν_{max}/cm^{-1} 3424 (w), 3223 (w), 2982 (w), 1603 (m), 1551 (m), 1491 (s), 1437 (m), 1366 (w), 1290 (m), 1231 (m), 1144 (m), 1082 (s), 1063 (s), 989 (w), 926 (w), 841 (m), 775 (w), 563 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 2935 (w), 1603 (s), 1457 (w), 1378 (w), 1336 (w), 1247 (w), 1145 (w), 1124 (w), 1048 (w), 992 (w), 925 (w), 741 (w), 484 (w), 456 (w), 327 (w), 226 (w). Found: C, 36.9; H, 6.2; N, 32.3. Calc. for $C_8H_{16}N_6S_2$: C, 36.8; H, 6.1; N, 32.2%. Mp: >198 °C (dec.).

Synthesis of 27: Intermediate **K** (0.452 g, 2.6 mol) was dissolved in DMF (2 mL) and filtered. 4,4-dimethyl-3-thiosemicarbazide (0.310 g, 2.6 mmol) was dissolved in DMF (4 mL), HCl (10%, 2 drops) was added and filtered. The two solutions were combined and left to stir for 5 h. De-ionised water (37 mL) was added and solution was put in the freezer (10 min). The precipitate was filtered off and washed with de-ionised water (50 mL, room temperature and 50 mL, 80°C). The crude product was dissolved in DMSO (3.5 mL), filtered and recrystallised with de-ionised water (60 mL). The precipitate was recovered by filtration, washed with de-ionised water (2 x 50 mL) and dried. A yellow solid (0.171 g) was recovered (24% yield). δ_H 10.18 (1 H, s, N-NH), 10.53 (1 H, s, N-NH), 8.38 (1 H, s, C-NH), 7.74 (1 H, s, C-NH), 3.22 (6 H, s, N-$(CH_3)_2$), 2.77 (2H, q, J = 7.6, C-CH_2), 2.08 (3 H, s, N=C-CH_3), 0.88 (3 H, t, J = 7.6, CH_2-CH_3). δ_C 182.39 (C=S), 179.32 (C=S), 153.32 (C=N), 147.88 (C=N), 42.95 (N-$(CH_3)_2$), 17.04 (CH_2), 12.01 (N=C-*C*H_3), 10.92 (CH_2-*C*H_3). IR: ν_{max}/cm^{-1} 3410 (w), 3229 (m), 3148 (w), 2974 (w), 2932 (w), 1593 (m), 1541 (m), 1483 (s), 1433 (s), 1260 (m), 1105 (s), 1076 (m), 1055 (s), 1020 (m), 989 (m), 926 (m), 843 (m), 511 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2934 (w), 1600 (s), 1583 (s), 1495 (w), 1458 (w), 1396 (w), 1367 (w), 1345 (w), 1246 (w), 1126 (m), 1111 (w), 991 (w), 732 (w), 633 (w), 603 (w), 461 (w), 386 (w), 332 (w). Found: C, 39.3; H, 6.2; N, 30.6. Calc. for $C_9H_{18}N_6S_2$: C, 39.4; H, 6.2; N, 30.6%. Mp: >180 °C (dec.).

Synthesis of 28: Intermediate **K** (0.277 g, 1.6 mmol) was dissolved in DMF (3 mL). 4-ethyl-3-thiosemicarbazide (0.191 g, 1.6 mmol) was dissolved in DMF (5 mL) and added HCl (10%, 1 drop) was added. The two solutions were combined and left to stir for 5 h. De-ionised water (14 mL) was added, the precipitate was filtered off and washed with de-ionised water (50 mL). The crude product was dissolved in DMSO (8 mL), filtered and recrystallised with de-ionised water (16 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL), ethanol (5 x 10 mL) and dried. A yellowish-white solid (0.168 g) was recovered (38% yield). δ_H 10.29 (1 H, s, N-NH), 10.19 (1 H, s, N-NH), 8.40 (1 H, s, C-NH), 8.60 (1 H, t, J = 6.0, H_2C-N*H*), 7.74 (1 H, s, C-NH), 3.54 (2 H, dq, J = 7.2, 6.0, HN-C*H*$_2$), 2.80 (2H, q, J = 7.2, C-CH$_2$), 2.14 (3 H, s, N=C-CH$_3$), 1.09 (3 H, t, J = 7.2, N-CH$_2$-C*H*$_3$), 0.84 (3 H, t, J =7.2, C-CH$_2$-C*H*$_3$). δ_C 179.28 (C=S), 177.90 (C=S), 152.19 (C=N), 147.86 (C=N), 39.35 (HN-CH$_2$), 17.04 (C-*C*H$_2$), 14.89 (N-CH$_2$-*C*H$_3$), 12.39 (N=C-*C*H$_3$), 11.44 (C-CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3428 (w), 3210 (w), 2982 (w), 1601 (m), 1537 (m), 1493 (s), 1435 (m), 1290 (m), 1213 (m), 1146 (m), 1080 (s), 1059 (m), 926 (w), 837 (m), 777 (w), 716 (w), 652 (w), 565 (m), 517 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 2934 (w), 1599 (s), 1589 (m), 1532 (w), 1457 (w), 1395 (w), 1368 (w), 1345 (w), 1247 (w), 1215 (w), 1120 (m), 1049 (w), 991 (w), 741 (w), 463 (w), 318 (w). Found: C, 39.5; H, 6.5; N, 30.55. Calc. for $C_9H_{18}N_6S_2$: C, 39.4; H, 6.6; N, 30.6% Mp: >218 °C (dec.).

Synthesis of 29: Intermediate **L** (0.599 g, 3.2 mmol) was dissolved in DMF (2 mL) and filtered. Thiosemicarbazide (0.292 g, 3.2 mmol) was dissolved in DMF (10 mL), HCl (10%, 2 drops) was added and filtered. The two solutions were combined and left to stir for 5 h. De-ionised water (24 mL) was added, the precipitate was filtered off and washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C). The crude product was dissolved in DMSO (31 mL), filtered and recrystallised with de-ionised water (62 mL). The precipitate was recovered by filtration, washed with de-ionised water (50 mL, room temperature and 50 mL, 80 °C) and dried. An off white solid (0.597 g) was recovered (72% yield). δ_H 10.29 (1 H, s, N-NH), 10.21 (1 H, s, N-NH), 8.39 (1 H, s, C-NH), 8.27 (1 H, q, J = 4.8, H_3C-N*H*), 7.80 (1 H, s, C-NH), 2.98 (3 H, d, J = 4.8, HN-C*H*$_3$), 2.87 (2H, q, J = 7.2, CH$_2$), 2.10 (3 H, s, N=C-CH$_3$), 0.85 (3 H, t, J =7.2, CH$_2$-C*H*$_3$). δ_C 179.35 (C=S), 178.96 (C=S), 152.89 (C=N), 147.48 (C=N), 31.80 (HN-CH$_3$), 17.36 (CH$_2$), 12.21 (N=C-*C*H$_3$), 11.53 (CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3408 (m), 3337 (w), 3229 (m), 3150 (m), 2978 (w), 2938 (w), 1603 (m), 1541 (m), 1491 (s), 1464 (s), 1439 (s), 1364 (m), 1227 (m), 1144 (m), 1082 (s), 1059 (s), 860 (m), 826 (m), 797 (m), 640 (m), 509 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2937 (w), 1604 (s), 1591 (m), 1591 (w), 1380 (w), 1341 (w), 1232 (w), 1144 (w), 1123 (m), 1024 (w), 985 (w), 737 (w), 675 (w), 481 (w), 460 (w). Found: C, 36.8; H, 6.2; N, 32.2. Calc. for $C_8H_{16}N_6S_2$: C, 36.9; H, 6.2; N, 32.3%. Mp: >202 °C (dec.).

Synthesis of 30: Intermediate **M** (0.322 g, 1.6 mmol) dissolved in DMF (2.5 mL) and filtered. Thiosemicarbazide (0.146 g, 1.6 mmol) dissolved in DMF (5.5 mL), added HCl (10%, 1 drop) and filtered. The two solutions were combined and left to stir for 5 h. De-ionised water (16 mL) was added, filtered off precipitate and washed with de-ionised water (50 mL, room temperature and 50 mL, 70°C). The crude product was dissolved in DMSO (14 mL), filtered and recrystallised with de-ionised water (28 mL). Filtered off precipitate, washed de-ionised water (50 mL) and dried. A white solid (0.237 g) was recovered (54% yield). δ_H 10.30 (1 H, s, N-NH), 10.15 (1 H, s, N-NH), 8.38 (1 H, s, C-NH), 8.28 (1 H, t, J = 6.0, H_2C-N*H*), 7.80 (1 H, s, C-NH), 3.55 (2 H, dq, J = 7.2, 6.0,HN-C*H*$_2$), 2.86 (2H, q, J = 7.2, C-CH$_2$), 2.10 (3 H, s, N=C-CH$_3$), 1.09 (3 H, t, J = 7.2, N-CH$_2$-C*H*$_3$), 0.86 (3 H, t, J = 7.2, C-CH$_2$-C*H*$_3$). δ_C 179.37 (C=S), 177.94 (C=S), 152.77 (C=N), 147.47 (C=N), 39.07 (HN-CH$_2$), 17.48 (C-*C*H$_2$), 14.89 (N-CH$_2$-*C*H$_3$), 12.20 (N=C-*C*H$_3$), 11.50 (C-CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3410 (w), 3333 (w), 3219 (m), 3152 (m), 2978 (w), 1601 (m), 1531 (m), 1493 (s), 1466 (s), 1439 (s), 1385 (m), 1292 (m), 1250 (m), 1207

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(s), 1167 (m), 1146 (m), 1080 (s), 1059 (s), 860 (m), 818 (m), 797 (m), 652 (m), 501 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2953 (w), 1602 (s), 1589 (m), 1533 (w), 1456 (w), 1393 (w), 1373 (w), 1347 (w), 1248 (w), 1214 (w), 1146 (w), 1122 (w), 1027 (w), 990 (w), 741 (w), 464 (w), 306 (w). Found: C, 39.3; H, 6.5; N, 30.55. Calc. for $C_9H_{18}N_6S_2$: C, 39.4; H, 6.6; N, 30.6%. Mp: >200 °C (dec.).

Synthesis of Copper Complexes

Cu(1),[22] **Cu(2)**,[33] **Cu(5)**,[22] **Cu(6)**,[22] **Cu(7)**,[22] **Cu(8)**,[22] **Cu(20)**,[22] **Cu(21)**[58] and **Cu(25)**[22] were synthesised as described previously. Copper complexes **Cu(3)**, **Cu(4)**, **Cu(10)**, **Cu(13)**, **Cu(18)**, **Cu(31)**, **Cu(32)**, **Cu(33)**, **Cu(34)**, **Cu(35)** and **Cu(36)** were not synthesised in this work; any data reported in Table 2 are derived from literature values. Other copper complexes were synthesised by a generic method as follows: Bis(thiosemicarbazone) pro-ligands (0.6 mmol) were added to a NaOH solution (1M, 13 mL, 50 °C), the minimum amount of DMF was added to achieve full dissolution. Copper (II) acetate monohydrate (0.140 g, 0.7 mmol) was dissolved in de-ionised water (5 mL). The solutions were combined and left to stir overnight. The precipitate was recovered via filtration, washed with methanol (3 x 10 mL) and de-ionised water (1 x 10 mL). The products were dried in air.

Data for Cu(9): HPLC R_t 7.17 min, >95%. ESI$^+$ MS: m/z for $[CuC_8H_{14}N_6S_2 + H]^+$ = 322.0090 (calc.), 322.0093 (found); TLC: R_f = 0.38;

Data for Cu(11): HPLC: R_t = 5.49 min, >95%; ESI$^+$ MS: m/z for $[CuC_8H_{14}N_6S_2 + H]^+$ = 322.0090 (calc.), 322.0098 (found).

Data for Cu(12): Yield: 61%. IR: ν_{max}/cm^{-1} 3294 (m), 1597 (w), 1547 (m), 1524 (s), 1497 (m), 1458 (s), 1435 (s), 1391 (s), 1368 (m), 1344 (m), 1317 (m), 1248 (m), 1219 (s), 1194 (s), 1179 (s), 1134 (m), 1123 (m), 926 (m), 897 (w), 881 (w), 808 (w), 758 (s), 687 (s), 664 (m), 631 (m), 610 (m), 586 (m), 507 (m), 446 (m), 419 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 1595 (w), 1540 (s), 1519 (m), 1466 (s), 1425 (w), 1348 (w), 1311 (w), 1242 (w), 1218 (m), 1131 (w), 993 (w), 922 (w), 820 (w), 664 (w), 590 (m), 485 (w), 358 (w). Found: C, 38.9; H, 3.7; N, 22.6. Calc. for $Cu_1C_{12}H_{14}N_6S_2$: C, 39.0; H, 3.8; N, 22.7%. Mp: >220 °C (decomp.). UV-Vis: λ_{max}/nm (DMSO) 320 (ε/dm^3 mol^{-1} cm^{-1} 18 900), 378 (13 100), 496 (9 700) and 540 (sh). MS (ESI): *m/z* (Calc.) 370.0092 (370.0096) {M + H$^+$}. HPLC: R_t = 19.17 min, >95%; ESI$^+$ MS: m/z for $[CuC_{12}H_{14}N_6S_2 + H]^+$ = 370.0090 (calc.), 370.0093 (found); TLC: R_f = 0.54.

Data for Cu(14): Yield: 63%. IR: ν_{max}/cm^{-1} 3321 (m), 2965 (w), 2926 (w), 1514 (s), 1483 (m), 1462 (s), 1391 (m), 1366 (s), 1339 (s), 1310 (s), 1258 (m), 1234 (s), 1179 (s), 1138 (s), 1059 (m), 1013 (m), 916 (m), 862 (m), 826 (m), 800 (m), 658 (m), 594 (m), 525 (s), 474 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1589 (w), 1538 (m), 1482 (s), 1460 (m), 1373 (w), 1312 (m), 1225 (m), 1008 (m), 931 (m), 661 (w), 632 (w), 596 (m), 351 (w). Found: C, 32.3; H, 4.7; N, 25.2. Calc. for $Cu_1C_9H_{16}N_6S_2$: C, 32.2; H, 4.8; N, 25.0%. UV-Vis: λ_{max}/nm (DMSO) 320 (ε/dm^3 mol^{-1} cm^{-1} 21 500), 360 (sh), 492 (9 500) and 540 (sh). MS (ESI): *m/z* (Calc.) 336.0255 (336.0252) {M + H$^+$}. ESI$^+$ MS: m/z for $[CuC_9H_{16}N_6S_2 + H]^+$ = 336.0247 (calc.), 336.0255 (found); HPLC: R_t = 11.72 min, > 95%; TLC: R_f = 0.34.

Data for Cu(15): HPLC: R_t = 28.9 min, >95%; ESI$^+$ MS: m/z for $[CuC_{13}H_{16}N_6S_2 + H]^+$ = 384.0247 (calc.), 384.0247 (found); TLC: R_f = 0.59.

Data for Cu(16): Yield: 69%. IR: ν_{max}/cm^{-1} 3289 (m), 3073 (m), 1632 (w), 1591 (m), 1541 (m), 1497 (s), 1408 (s), 1368 (s), 1319 (s), 1256 (m), 1244 (m), 1184 (s), 1150 (s), 928 (m), 891 (m), 864 (m), 847 (m), 820 (m), 750 (s), 735 (m), 685 (s), 640 (m), 617 (m), 600 (m), 584 (s), 505 (s), 463 (s). Raman

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(632.81 nm): ν_{max}/cm^{-1} 1528 (s), 1470 (s), 1431 (m), 1314 (w), 1237 (m), 1185 (w), 996 (w), 929 (w), 670 (w), 618 (w), 599 (w), 359 (w), 300 (w). Found: C, 37.2; H, 3.3; N, 23.4. Calc. for $Cu_1C_{11}H_{12}N_6S_2$: C, 37.1; H, 3.4; N, 23.6%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 21 000), 372 (13 300), 494 (9 600) and 540 (sh). MS (ESI): *m/z* (Calc.) 355.9935 (355.9939) {M + H$^+$}.

Data for Cu(17): Yield: 61%. IR: ν_{max}/cm^{-1} 3279 (w), 3213 (w), 2932 (w), 1597 (m), 1582 (w), 1545 (m), 1493 (s), 1433 (s), 1346 (s), 1321 (s), 1279 (s), 1244 (m), 1196 (s), 1148 (s), 1043 (m), 934 (m), 891 (w), 847 (m), 822 (m), 745 (s), 685 (s), 610 (m), 584 (m), 503 (s), 484 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 1576 (m), 1507 (s), 1470 (s), 1429 (m), 1383 (w), 1351 (w), 1312 (w),1273 (m), 1243 (m), 1192 (w), 994 (w), 932 (m), 676 (w), 600 (m), 542 (w), 479 (w), 368 (w), 130 (w). Found: C, 38.9; H, 3.7; N, 22.6. Calc. for $Cu_1C_{12}H_{14}N_6S_2$: C, 39.0; H, 3.8; N, 22.7%. UV-Vis: λ_{max}/nm (DMSO) 318 (ε/dm^3 mol^{-1} cm^{-1} 20 600), 380 (sh), 492 (10 100) and 540 (sh). MS (ESI): *m/z* (Calc.) 370.0092 (370.0096) {M + H$^+$}. HPLC: R_t = 16.05 min, >95%; ESI$^+$ MS: m/z for $[CuC_{12}H_{14}N_6S_2 + H]^+$ = 370.0090 (calc.), 370.0095 (found); TLC: R_f = 0.41.

Data for Cu(19): HPLC: R_t = 27.57 min, >95%; ESI$^+$ MS: m/z for $[CuC_{13}H_{16}N_6S_2 + H]^+$ = 384.0247 (calc.), 384.0247 (found); TLC: R_f = 0.52.

Data for Cu(22): HPLC: R_t = 16.01 min, >95%; ESI$^+$ MS: m/z for $[CuC_9H_{16}N_6S_2 + H]^+$ = 336.0247 (calc.), 336.0249; TLC: R_f = 0.42.

Data for Cu(23): Yield: 59%. IR: ν_{max}/cm^{-1} 3458 (w), 3321 (m), 3287 (w), 3136 (w), 1626 (m), 1549 (m), 1504 (m), 1443 (s), 1396 (m), 1364 (m), 1344 (s), 1287 (s), 1221 (s), 1188 (m), 1150 (m), 1099 (m), 1057 (m), 1038 (m), 984 (m), 841 (m), 756 (w), 733 (m), 700 (m), 629 (m), 610 (m), 563 (m), 527 (m), 509 (s), 419 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1542 (m), 1496 (s), 1379 (w), 1284 (s), 1184 (w), 998 (w), 837 (w), 697 (w), 609 (w), 588 (w), 390 (w), 346 (w), 316 (w), 271 (w), 253 (w), 138 (w). Mp: >266 ^{o}C (decomp.). UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 22 500), 350 (sh), 476 (6 900) and 520 (sh). MS (ESI): *m/z* (Calc.) 307.9935 (307.9939) {M + H$^+$}. HPLC: R_t = 3.46 min, >95%; ESI$^+$ MS: m/z for $[CuC_7H_{12}N_6S_2 + H]^+$ = 307.9934 (calc.), 307.9935 (found); TLC: R_f = 0.39.

Data for Cu(24): Yield: 53%. IR: ν_{max}/cm^{-1} 3426 (w), 3289 (w), 3157 (w), 2918 (w), 1622 (m), 1589 (w), 1541 (m), 1499 (m), 1439 (m), 1387 (s), 1362 (s), 1296 (s), 1258 (s), 1217 (s), 1171 (s), 1140 (m), 1115 (s), 1055 (s), 999 (m), 908 (s), 841 (s), 762 (m), 706 (m), 610 (m), 596 (m), 515 (m), 430 (s). Raman (532.00 nm): ν_{max}/cm^{-1} 2837 (w), 2807 (w), 2144 (w), 1901 (w), 1804 (w), 1598 (w), 1543 (m), 1497 (m), 1298 (s), 1263 (w), 1204 (w), 1003 (w), 921 (w), 846 (w), 602 (w). Found: C, 29.7; H, 4.2; N, 25.9. Calc. for $Cu_1C_8H_{14}N_6S_2$: C, 29.85; H, 4.4; N, 26.1%. UV-Vis: λ_{max}/nm (DMSO) 313(ε/dm^3 mol^{-1} cm^{-1} 17 900), 350 (sh), 481 (6 700) and 540 (sh). MS (ESI): *m/z* (Calc.) 322.0097 (322.0096) {M + H$^+$}. HPLC: R_t = 6.43 min, > 95%; ESI$^+$ MS: m/z for $[CuC_8H_{14}N_6S_2 + H]^+$ = 322.0090 (calc.), 322.0085 (found).

Data for Cu(26): Yield:15%. IR: ν_{max}/cm^{-1} 3292 (w), 3146 (w), 1626 (w), 1541 (m), 1518 (w), 1479 (m), 1445 (m), 1391 (m), 1335 (w), 1217 (m), 1190 (m), 1152 (m), 1107 (w), 1061 (w), 951 (w), 779 (w), 727 (w), 592 (m). Raman (532.00 nm): ν_{max}/cm^{-1} 2127 (w), 2075 (w), 1537 (m), 1515 (m), 1480 (w), 1335 (m), 1249 (m), 1025 (w), 794 (w), 604 (m). Found: C, 29.7; H, 4.3; N, 26.0. Calc. for $Cu_1C_8H_{14}N_6S_2$: C, 29.85; H, 4.4; N, 26.1%. UV-Vis: λ_{max}/nm (DMSO) 312(ε/dm^3 mol^{-1} cm^{-1} 11 300), 350 (sh), 480 (4 100) and 530 (sh). MS (ESI): *m/z* (Calc.) 322.0135 (322.0096) {M + H$^+$}. HPLC: R_t = 5.36 min, >95%; ESI$^+$ MS: m/z for $[CuC_8H_{14}N_6S_2 + H]^+$ = 322.0090 (calc.), 322.0080 (found); TLC: R_f = 0.53.

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Data for Cu(27): Yield: 43%. IR: ν_{max}/cm^{-1} 3360 (w), 3285 (w), 3129 (w), 3129 (w), 2931 (w), 1632 (m), 1585 (w), 1537 (m), 1493 (m), 1456 (s), 1389 (s), 1321 (m), 1300 (s), 1258 (s), 1240 (s), 1213 (s), 1169 (s), 1115 (s), 1061 (m), 957 (m), 910 (m), 847 (w), 795 (m), 706 (m), 631 (m), 598 (m), 536 (s), 517 (s), 496 (s), 428 (s). Raman (532.00 nm): ν_{max}/cm^{-1} 1590 (w), 1536 (w), 1497 (w), 1320 (w), 1302 (w), 1247 (w), 633 (w), 598 (w). Mp: >220 ^{o}C (decomp.). Found: C, 32.4; H, 4.8; N, 24.9. Calc. for $Cu_1C_9H_{16}N_6S_2$: C, 32.2; H, 4.8; N, 25.0%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 23 400), 350 (sh), 484 (8 800) and 530 (sh). MS (ESI): *m/z* (Calc.) 336.0247 (336.00252) {M + H$^+$}. HPLC: R_t = 11.96 min, >95%; ESI$^+$ MS: m/z for $[CuC_9H_{16}N_6S_2 + H]^+$ = 336.0247 (calc.), 336.0247 (found); TLC: R_f = 0.57.

Data for Cu(28): Yield: 43%. IR: ν_{max}/cm^{-1} 3347 (w), 3157 (w), 2963 (w), 1628 (w), 1587 (w), 1537 (m), 1506 (m), 1476 (m), 1445 (m), 1416 (s), 1366 (m), 1335 (m), 1310 (m), 1221 (s), 1184 (m), 1142 (m), 1061 (m), 955 (w), 787 (m), 689 (m), 597 (m), 419 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3329 (w), 1584 (w), 1533 (s), 1504 (m), 1479 (s), 1371 (m), 1352 (m), 1330 (m), 1248 (m), 1230 (m), 1172 (m), 1030 (w), 999 (w), 957 (w), 787 (w), 602 (m), 338 (m), 317 (w), 261 (w), 221 (w), 157 (m). Mp: >210 ^{o}C (decomposed). Found: C, 32.3; H, 4.8; N, 24.85. Calc. for $Cu_1C_9H_{16}N_6S_2$: C, 32.2; H, 4.8; N, 25.0%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 25 500), 350 (sh), 480 (8 200) and 530 (sh). MS (ESI): *m/z* (Calc.) 336.0287 (336.0252) {M + H$^+$}. HPLC: R_t = 8.12 min, >95%; ESI$^+$ MS: m/z for $[CuC_9H_{16}N_6S_2 + H]^+$ = 336.0247 (calc.), 336.0287 (found); TLC: R_f = 0.47.

Data for Cu(29): Yield: 54%. IR: ν_{max}/cm^{-1} 3281 (w), 3119 (w), 1643 (w), 1622 (w), 1541 (m), 1504 (m), 1441 (s), 1350 (m), 1281 (m), 1240 (m), 1215 (s), 1186 (s), 1150 (m), 1101 (m), 1076 (m), 1028 (m), 943 (m), 800 (m), 719 (m), 638 (m), 615 (m) 471 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1582 (w), 1532 (m), 1497 (s), 1433 (w), 1380 (w), 1321 (w), 1281 (m), 1238 (m), 1190 (w), 1031 (w), 987 (w), 943 (w), 848 (w), 801 (w), 702 (w), 610 (w), 395 (w), 351 (w), 320 (w), 139 (w). Found: C, 29.8; H, 4.5; N, 26.0. Calc. for $Cu_1C_8H_{14}N_6S_2$: C, 29.85; H, 4.4; N, 26.1%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 16 600), 350 (sh), 478 (5 200) and 520 (sh). MS (ESI): *m/z* (Calc.) 322.0092 (322.0096) {M + H$^+$}. HPLC: R_t = 4.96 min, >95%; ESI$^+$ MS: m/z for $[CuC_8H_{14}N_6S_2 + H]^+$ = 322.0090 (calc.), 322.0093 (found); TLC: R_f = 0.53.

Data for Cu(30): Yield: 34%. IR: ν_{max}/cm^{-1} 3374 (w), 3339 (m), 3152 (w), 2972 (w), 1630 (m), 1593 (w), 1539 (w), 1508 (m), 1479 (m), 1437 (s), 1381 (m), 1329 (m), 1304 (m), 1261 (w), 1236 (m), 1211 (s), 1173 (m), 1142 (m), 1103 (m), 1032 (m), 951 (m), 841 (w), 820 (w), 802 (w), 731 (m), 600 (m), 540 (m), 505 (s), 484 (s), 415 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1591 (w), 1533 (s), 1482 (m), 1460 (m), 1374 (w), 1355 (w), 1324 (m), 1299 (m), 1228 (m), 1171 (w), 1033 (m), 951 (w), 840 (w), 778 (w), 602 (w), 336 (w), 265 (w), 165 (m). Elemental analysis: C, 32.3; H, 4.8; N, 24.9. Calc. for $Cu_1C_9H_{16}N_6S_2$: C, 32.2; H, 4.8; N, 25.0%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 22 100), 350 (sh), 480 (7 100) and 530 (sh). MS (ESI): *m/z* (Calc.) 336.0297 (336.0252) {M + H$^+$}. HPLC: R_t = 7.68 min, >95%; ESI$^+$ MS: m/z for $[CuC_9H_{16}N_6S_2 + H]^+$ = 336.0247 (calc.), 336.0248 (found); TLC: R_f = 0.54

Synthesis of Zinc Complexes

Exemplar zinc bis(thiosemicarbazonate) complexes listed below were synthesised by a generic method as follows: the bis(thiosemicarbazone) pro-ligand (0.6 mmol) was added to ethanol (15 mL). Anhydrous zinc (II) acetate (0.128 g, 0.7 mmol) was added to the suspension. The suspension was then brought to reflux for 2 h. The yellow-orange precipitate was recovered via filtration, washed with ethanol (1 x 15 mL) and diethyl ether (5 x 15 mL). The solid was dried in air.

Data for Zn(12): Yield: 48%. δ_H 9.48 (1 H, s, Ph-NH), 7.76 (1 H, s, N=CH), 7.72 (2 H, m, $H_{(2,6)}$ aryl), 7.43 (1 H, s, CH_3-NH), 7.43 (2 H, t, J =7.2, $H_{(3,5)}$ aryl), 6.89 (1 H, d, J = 7.2, $H_{(4)}$ aryl), 2.81 (3 H, s, N-CH_3), 2.10 (3 H, s, N=C-CH_3). δ_C 141.87 (C=N), 141.35 ($C_{(1)}$ aryl), 128.86 ($C_{(3,5)}$ aryl), 122.31 ($C_{(4)}$ aryl), 120.88 ($C_{(2,6)}$ aryl), 29.69 (N-CH_3), 16.26 (N=C-CH_3). IR: ν_{max}/cm^{-1} 3451 (w), 3267 (w), 3130 (w), 3071 (w), 1597 (w), 1545 (m), 1493 (m), 1477 (m), 1450 (m), 1416 (s), 1398 (s), 1348 (m), 1319 (m), 1308 (m), 1263 (m), 1242 (m), 1221 (s), 1171 (s), 1130 (s), 1072 (m), 1030 (m), 997 (m), 959 (m), 922 (m), 895 (m), 885 (m), 831 (m), 824 (m), 795 (m), 743 (s), 683 (s), 658 (m), 617 (s), 584 (s), 501 (s), 474 (m), 430 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 3273 (w)1619 (w), 1602 (w), 1549 (m), 1536 (s), 1477 (s), 1454 (m), 1516 (m), 1370 (w), 1347 (w), 1318 (w), 1310 (m), 1246 (m), 1225 (m), 1187 (w), 1132 (m), 1034 (w), 996 (w), 923 (m), 831 (w), 656 (w), 618 (w), 591 (w), 583 (w), 472 (w), 457 (w), 348 (w). Found: C, 38.8; H, 3.9; N, 22.6. Calc. for $Zn_1C_{12}H_{14}N_6S_2$: C, 39.0; H, 3.8; N, 22.7%. UV-Vis: λ_{max}/nm (DMSO) 342 (ε/dm^3 mol^{-1} cm^{-1} 18 200) and 450 (15 800). MS (ESI): *m/z* (Calc.) 371.0093 (371.0091) {M + H^+}.

Data for Zn(14): Yield: 42%. δ_H = 7.53 (1 H, s, N=CH), 7.28 (1 H, s, H_2C-NH), 3.15 (6 H, s, HN-(C*H*$_3$)$_2$), 2.05 (3 H, s, N=C-CH_3), 1.06 (3 H, t, J= 7.2, H_2C-C*H*$_3$). δ_C 180.44 (C-S), 137.31 (C=N), 37.46 (N-CH_2), 16.27 (N=C-*C*H$_3$), 15.16 (H_2C-*C*H$_3$). IR: ν_{max}/cm^{-1} 3304 (m), 2970 (w), 2928 (w), 2870 (w), 1514 (m), 1508 (m), 1437 (s), 1375 (s), 1339 (s), 1317 (s), 1263 (s), 1248 (s), 1217 (s), 1179 (s), 1128 (s), 1053 (m), 934 (m), 907 (s), 891 (s), 818 (m), 723 (m), 650 (m), 621 (m), 613 (m), 586 (m), 559 (m), 540 (m), 457 (m), 417 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3304 (w), 1611 (w), 1541 (s), 1499 (s), 1482 (s), 1450 (s), 1404 (w), 1378 (w), 1369 (w), 1321 (s), 1249 (w), 1219 (s), 1182 (w), 1133 (w), 1122 (w), 1002 (m), 931 (s), 892 (w), 725 (w), 651 (w), 586 (m), 493 (w), 456 (w), 418 (w), 332 (w), 279 (w). Found: C, 32.1; H, 4.7; N, 25.0. Calc. for $Zn_1C_9H_{16}N_6S_2$: C, 32.0; H, 4.8; N, 24.9%. UV-Vis: λ_{max}/nm (DMSO) 322 (ε/dm^3 mol^{-1} cm^{-1} 11 900) and 454 (13 700). MS (ESI): *m/z* (Calc.) 337.0272 (337.0248) {M + H^+}.

Data for Zn(16): Yield: 33%. δ_H 9.34 (1 H, s, Ph-NH), 7.77 (2 H, m, $H_{(2,6)}$ aryl), 7.54 (1 H, s, N=CH), 7.36 (2 H, s, C-NH), 7.19 (2 H, t, J=7.2, $H_{(3,5)}$ aryl), 6.86 (1 H, t, J=7.2, $H_{(4)}$ aryl), 2.17 (s, 3 H, CH_3). δ_C 177.13 (C-S), 172.93 (C-S), 147.94 (C=N), 141.71 (C=N), 135.66 ($C_{(1)}$ aryl), 128.88 ($C_{(3,5)}$ aryl), 121.85 ($C_{(4)}$ aryl), 120.33 ($C_{(2,6)}$ aryl), 17.02 (CH_3). IR: ν_{max}/cm^{-1} 3402 (w), 3316 (w), 1612 (m), 1537 (m), 1514 (m), 1495 (m), 1456 (m), 1408 (s), 1327 (m), 1314 (m), 1256 (w), 1233 (w), 1192 (w), 1150 (m), 1026 (w), 928 (w), 901 (w), 851 (w), 814 (w), 752 (m), 691 (m), 615 (m), 552 (m), 503 (m), 465 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 2918 (w), 1635 (w), 1600 (w), 1551 (s), 1516 (m), 1474 (m), 1376 (w), 1334 (w), 1312 (w), 1229 (m), 1193 (w), 1155 (w), 999 (w), 930 (w), 850 (w), 741 (w), 698 (w), 647 (w), 617 (w), 599 (w), 539 (w), 493 (w), 360 (w), 324 (w), 302 (w). Mp: >250 ^{o}C (decomp.). UV-Vis: λ_{max}/nm (DMSO) 328 (ε/dm^3 mol^{-1} cm^{-1} 9 600) and 452 (12 900).

Data for Zn(17): Yield: 48%. δ_H 9.36 (1 H, s, Ph-NH), 7.77 (2 H, m, $H_{(2,6)}$ aryl), 7.63 (2 H, s, H_3C-N*H* and N=C*H*), 7.20 (2 H, t, J=7.2, $H_{(3,5)}$ aryl), 6.87 (1 H, t, J=7.2, $H_{(4)}$ aryl), 2.78 (3 H, s, N-CH_3), 2.18 (3 H, s, N=C-CH_3). δ_C = 141.71 ($C_{(1)}$ aryl), 128.90 ($C_{(3,5)}$ aryl), 121.89 ($C_{(4)}$ aryl), 120.34 ($C_{(2,6)}$ aryl), 17.02 (N=C-*C*H$_3$). IR: ν_{max}/cm^{-1} 3316 (w), 3265 (w), 3210 (w), 3125 (w), 3051 (w), 3005 (w), 2916 (w), 1597 (m), 1543 (m), 1504 (s), 1493 (s), 1464 (s), 1429 (s), 1352 (s), 1319 (s), 1302 (s), 1240 (m), 1200 (s), 1182 (m), 1173 (m), 1148 (m), 1119 (m), 1076 (m), 1042 (m), 932 (m), 868 (m), 845 (m), 820 (m), 750 (s), 387 (m), 675 (m), 627 (m), 608 (m), 592 (m), 581 (m), 530 (m), 503 (m), 469 (m), 419 (m). Raman (632.81 nm): ν_{max}/cm^{-1} 3319 (w), 3034 (w), 1616 (w), 1599 (w), 1540 (w), 1507 (s), 1462 (s), 1427 (w), 1382 (w), 1316 (m), 1298 (m), 1243 (s), 1184 (m), 994 (w), 933 (s),869 (w), 845 (w), 720 (w), 668

(w), 609 (w), 593 (m), 535 (w), 461 (w), 414 (w), 384 (w), 353 (w), 328 (w), 287 (w), 239 (w). Found: C, 38.85; H, 3.8; N, 22.6. Calc. for $Zn_1C_{12}H_{14}N_6S_2$: C, 38.8; H, 3.8; N, 22.6%. Mp: >270 °C (decomposed). UV-Vis: λ_{max}/nm (DMSO) 330 (ε/dm^3 mol^{-1} cm^{-1} 13 100) and 454 (18 800). MS (ESI): *m/z* (Calc.) 371.0093 (371.0091) {M + H$^+$}.

Data for Zn(23): Yield: 55%. δ_H 7.16 (1 H, s, H_3C-N*H*), 6.86 (2 H, s, C-NH), 2.77 (3 H, m, HN-C*H*$_3$), 2.15 (3 H, s, N=C-CH$_3$), 2.12 (3 H, s, N=C-C*H*$_3$). δ_C 178.47 (C-S), 144.60 (C=N), 29.72 (HN-CH$_3$), 14.46 (N=C-CH$_3$).). IR: ν_{max}/cm^{-1} 3464 (w), 3404 (w), 3352 (m), 3277 (w), 3134 (m), 1628 (m), 1607 (w), 1547 (m), 1516 (m), 1487 (m), 1431 (s), 1396 (s), 1375 (s), 1315 (m), 1300 (m), 1223 (s), 1184 (m), 1153 (m), 1094 (m), 1057 (m), 999 (m), 982 (m), 831 (s), 727 (s), 696 (m), 654 (m), 588 (m), 522 (m), 501 (m), 444 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3351 (w), 2927 (w), 1614 (w), 1538 (s), 1483 (s), 1454 (w), 1425 (w), 1317 (m), 1302 (m), 1264 (w), 1236 (m), 1192 (m), 999 (w), 831 (w), 785 (w), 718 (w), 653 (w), 593 (w), 450 (w), 394 (w), 325 (m), 290 (w). UV-Vis: λ_{max}/nm (DMSO) 312 (ε/dm^3 mol^{-1} cm^{-1} 13 900) and 432 (12 800).

Data for Zn(24): Yield: 64%. δ_H = 6.86 (2 H, s, C-NH), 3.14 (6 H, s, N-(CH$_3$)$_2$), 2.15 (3 H, s, N=C-CH$_3$), 2.12 (3 H, s, N=C-CH$_3$). δ_C 178.38 (C-S), 178.12 (C-S), 145.25 (C=N), 144.78 (C=N), 11.96 (N=C-*C*H$_3$), 11.70 (N=C-*C*H$_3$). IR: ν_{max}/cm^{-1} 3422 (w), 3283 (w), 3159 (w), 2916 (w), 1622 (m), 1601 (m), 1541 (m), 1501 (m), 1433 (s), 1389 (s), 1375 (s), 1364 (s), 1294 (s), 1261 (s), 1207 (m), 1165 (s), 1136 (m), 1107 (m), 1055 (m), 903 (s), 835 (s), 758 (m), 700 (m), 619 (m), 590 (m), 567 (w), 519 (m), 478 (m), 457 (m), 432 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 2916 (w), 1609 (w), 1543 (m), 1508 (s), 1466(w), 1434 (w), 1375 (w), 1327 (w), 1293 (s), 1264 (w), 1205 (w), 1171 (w), 1141 (w), 1006 (w), 989 (w), 835 (w), 752 (w), 698 (w), 626 (w), 567 (w), 588 (w), 567 (w), 429 (w), 380 (w), 335 (w), 294 (w). Found: C, 29.6; H, 4.4; N, 25.8. Calc. for $Zn_1C_8H_{14}N_6S_2$: C, 29.7; H, 4.7; N, 26.0%. Mp: >250 °C (decomp.). UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 12 600) and 442 (12 900).

Data for Zn(26): Yield: 51%. δ_H 7.18 (1 H, s, C-NH), 6.87 (2 H, s, N*H*$_2$), 2.77 (3 H, m, HN-C*H*$_3$), 2.64 (2H, q, J= 7.6, C-CH$_2$), 2.13 (3 H, s, N=C-CH$_3$), 1.00 (3 H, t, J=7.6, CH$_2$-C*H*$_3$). δ_C 178.47 (C-S), 144.04 (C=N), 29.79 (HN-CH$_3$), 20.93 (C-*C*H$_2$), 14.22 (N=C-*C*H$_3$), 10.83 (CH$_2$-*C*H$_3$).). IR: ν_{max}/cm^{-1} 3445 (w), 3399 (w), 3275 (w), 3140 (w), 2972 (w), 2928 (w), 1624 (w), 1605 (w), 1541 (m), 1489 (m), 1425 (s), 1395 (s), 1333 (m), 1294 (m), 1231 (m), 1204 (m), 1180 (m), 1148 (m), 1098 (m), 1059 (m), 953 (m), 841 (m), 787 (m), 772 (m), 723 (m), 646 (m), 621 (m), 596 (m), 532 (m), 501 (m), 459 (m), 415 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3446 (w), 2972 (w), 2923 (w), 1611 (w), 1538 (m), 1492 (s), 1426 (w), 1397 (w), 1331 (w), 1298 (w), 1244 (w), 1233 (w), 1206 (w), 1184 (w), 1153 (w), 1083 (w), 989 (w), 954 (w), 840 (w), 783 (w), 594 (w), 429 (w), 396 (w), 328 (w), 244 (w). Found: C, 29.8; H, 4.5; N, 25.9. Calc. for $Zn_1C_8H_{14}N_6S_2$: C, 29.7; H, 4.4; N, 26.0%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 13 900) and 436 (12 800). MS (ESI): *m/z* (Calc.) 323.0102 (323.0091) {M + H$^+$}.

Data for Zn(27): Yield: 9%. δ_H 6.87 (2 H, s, C-NH), 3.15 (6 H, s, N-(CH$_3$)$_2$), 2.66 (2H, q, J= 7.6, C-CH$_2$), 2.14 (3 H, s, N=C-CH$_3$), 1.02 (3 H, t, J=7.6, CH$_2$-C*H*$_3$). δ_C 178.40 (C-S), 178.31 (C-S), 149.70 (C=N), 144.23 (C=N), 20.96 (C-*C*H$_2$), 14.20 (N=C-*C*H$_3$), 10.71 (CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3418 (w), 3285 (w), 3157 (w), 2922 (w), 1620 (w), 1597 (w), 1539 (m), 1495 (m), 1429 (m), 1391 (s), 1327 (m), 1298 (m), 1265 (s), 1244 (m), 1207 (s), 1169 (m), 1142 (m), 1107 (m), 1053 (m), 949 (m), 905 (s), 839 (m), 785 (m), 745 (m), 700 (m), 669 (m), 617 (m), 588 (m), 482 (s), 461 (s), 432 (s). Raman (632.81 nm):

ν_{max}/cm^{-1} 3285 (w), 2919 (w), 1603 (w), 1539 (s), 1500 (s), 1457 (m), 1443 (m), 1385 (w), 1367 (w), 1330 (s), 1302 (s), 1266 (w), 1244 (m), 1207 (w), 1174 (w), 1081 (w), 1029 (w), 996 (w), 951 (w), 905 (w), 842 (w), 783 (w), 740 (w), 700 (w), 672 (w), 620 (w), 588 (m), 495 (w), 430 (w), 400 (w), 379 (w), 327 (w), 290 (w), 259(w). Found: C, 32.1; H, 4.7; N, 24.75. Calc. for $Zn_1C_9H_{16}N_6S_2$: C, 32.0; H, 4.8; N, 24.9%. UV-Vis: λ_{max}/nm (DMSO) 318 (ε/dm^3 mol^{-1} cm^{-1} 12 200) and 446 (13 000).

Data for Zn(28): Yield: 33%. δ_H 7.23 (1 H, t, J= 6.0, H_2C-N*H*), 6.84 (2 H, s, C-NH), 3.31 (2 H, m, HN-C*H*$_2$), 2.64 (2H, q, J= 7.6, C-CH$_2$), 2.14 (3 H, s, N=C-CH$_3$), 1.06 (3 H, t, J=7.6, N-CH$_2$-C*H*$_3$,), 1.00 (3 H, t, J=7.6, C-CH$_2$-C*H*$_3$). δ_C 178.44 (C-S), 144.13 (C=N), 37.56 (HN-CH$_2$), 20.95 (C-*C*H$_2$), 15.27 (N-CH$_2$-*C*H$_3$), 14.20 (N=C-*C*H$_3$), 11.01 (C-CH$_2$-*C*H$_3$).). IR: ν_{max}/cm^{-1} 3422 (m), 3285 (w), 3161 (w), 2976 (w), 2932 (w), 2870 (w), 1603 (m), 1541 (m), 1466 (s), 1425 (s), 1383 (m), 1369 (m), 1350 (m), 1329 (m), 1296 (m), 1231 (m), 1204 (s), 1171 (m), 1144 (m), 1059 (m), 951 (m), 783 (m), 723 (m), 656 (w), 530 (w), 442 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 1614 (m), 1539 (s), 1490 (s), 1468 (m), 1423 (m), 1368 (m), 1350 (m), 1328 (m), 1299 (m), 1243 (m), 1231 (m), 1206 (m), 1178 (m), 1030 (w), 990 (w), 953 (w), 782 (w), 719 (w), 655 (w), 594 (w), 585 (w), 409 (w), 391 (w), 344 (w), 290 (w). Found: C, 32.2; H, 4.6; N, 24.8. Calc. for $Zn_1C_9H_{16}N_6S_2$: C, 32.0; H, 4.8; N, 24.9%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 12 900) and 438 (12 100). MS (ESI): *m/z* (Calc.) 337.0276 (337.0248) {M + H$^+$}.

Data for Zn(29): Yield: 34%. δ_H 7.16 (1 H, s, H_3C-N*H*), 6.88 (2 H, s, C-NH), 2.78 (3 H, m, HN-C*H*$_3$), 2.63 (2H, q, J= 7.6, C-CH$_2$), 2.17 (3 H, s, N=C-CH$_3$), 0.99 (3 H, t, J=7.6, CH$_2$-C*H*$_3$). δ_C 178.76 (C-S), 149.74 (C=N), 29.73 (HN-CH$_3$), 20.83 (C-*C*H$_2$), 14.18 (N=C-*C*H$_3$), 11.36 (CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3242 (m), 3103 (m), 2967 (w), 1643 (m), 1547 (m), 1508 (m), 1435 (s), 1366 (s), 1327 (s), 1283 (s), 1242 (m), 1204 (s), 1180 (s), 1148 (s), 1096 (m), 1074 (s), 1030 (s), 943 (s), 839 (m), 799 (m), 745 (m), 698 (m), 658 (s), 611 (s), 584 (s), 530 (s), 465 (s). Raman (632.81 nm): ν_{max}/cm^{-1} 3252 (w), 1607 (w), 1545 (w), 1508 (s), 1430 (w), 1379 (w), 1327 (w), 1288 (m), 1243 (m), 1206 (w), 1186 (w), 1031 (w), 984 (w), 943 (w), 843 (w), 799 (w), 701 (w), 591 (w), 525 (w), 386 (w), 320 (w), 229 (w). Found: C, 29.7; H, 4.3; N, 26.0. Calc. for $Zn_1C_8H_{14}N_6S_2$: C, 29.7; H, 4.4; N, 26.0%. Mp: >245 ^{o}C (decomp.). UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 12 800) and 436 (11 800). MS (ESI): *m/z* (Calc.) 323.0102 (323.0091) {M + H$^+$}.

Data for Zn(30): Yield: 33%. δ_H 7.14 (1 H, s, H_2C-N*H*), 6.75 (2 H, s, C-N*H*), 3.31 (2 H, m, HN-C*H*$_2$), 2.61 (2H, q, , J= 7.2, C-CH$_2$), 2.15 (3 H, s, N=C-CH$_3$), 1.05 (3 H, t, J=7.2, N-CH$_2$-C*H*$_3$,), 0.97 (3 H, t, J=7.2, C-CH$_2$-C*H*$_3$). δ_C 178.63 (C-S), 149.70 (C=N), 37.48 (HN-CH$_2$), 20.83 (C-*C*H$_2$), 15.13 (N-CH$_2$-*C*H$_3$), 14.12 (N=C-*C*H$_3$), 11.31 (C-CH$_2$-*C*H$_3$). IR: ν_{max}/cm^{-1} 3424 (w), 3283 (w), 3163 (w), 2978 (w), 2870 (w), 1603 (m), 1543 (m), 1477 (m), 1466 (m), 1425 (s), 1371 (m), 1329 (m), 1298 (m), 1258 (m), 1233 (m), 1204 (s), 1171 (m), 1146 (m), 1022 (m), 945 (m), 839 (m), 802 (m), 775 (m), 725 (m), 654 (m), 588 (m), 538 (m), 438 (s), 432 (s).). Raman (784.15 nm): ν_{max}/cm^{-1} 1614 (w), 1541 (s), 1492 (s), 1465 (w), 1423 (w), 1372 (w), 1355 (w), 1327 (w), 1303 (w), 1259 (w), 1234 (m), 1204 (m), 1156 (w), 1023 (w), 999 (w), 947 (w), 839 (w), 803 (w), 777 (w), 719 (w), 589 (w), 412 (w), 382 (w), 320 (w), 287 (w). Found: C, 31.7; H, 4.7; N, 24.7. Calc. for $Zn_1C_9H_{16}N_6S_2$: C, 32.0; H, 4.8; N, 24.9%. UV-Vis: λ_{max}/nm (DMSO) 314 (ε/dm^3 mol^{-1} cm^{-1} 13 900) and 436 (12 800). MS (ESI): *m/z* (Calc.) 337.0245 (337.0248) {M + H$^+$}.

Transmetallation Reactions

Zn(14) (0.027g (0.08 mmol) was dissolved in DMSO (1 mL). Copper acetate monohydrate (0.018g 0.09 mmol) was dissolved in deionised water (1 mL). The solutions were combined

and stirred for 5 mins. The solution changed rapidly to a brown colour. The precipitate was recovered by filtration, washed with water (10 mL) and diethyl ether (10 mL) and dried in air. A brown solid (0.026 g) was recovered (91% yield). **Cu(17)** and **Cu(29)** were prepared similarly in yields of 49% and 74% respectively. Spectroscopic properties of these three copper complexes matched those of their counterparts synthesised as described above.

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Conflict of interest

There are no conflicts to declare

Footnote

Electronic supplementary information (ESI) available: Contains NMR, IR, Raman and Mass spectra.

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A library of copper(II) bis(thiosemicarbazone) complexes offers independently controlled redox potential and lipophilicity for optimal ^{64}Cu optimal PET tracer design.